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CANNABINOID RECEPTOR INVERSE AGONISTS AND NEUTRAL ANTAGONISTS AS THERAPEUTIC AGENTS FOR THE TREATMENT OF BONE DISORDERS

Abstract:

Abstract of WO2004078261

The present invention pertains to cannabinoid (CB) receptor inverse agonists and neutral antagonists, and especially CB1 and CB2 inverse agonists and neutral antagonists; such as, for example, certain pyrazole compounds; their use in the inhibition of osteoclasts (for example, the inhibition of the survival, formation, and/or activity of osteoclasts), and/or in the inhibition of bone resor fd9 ption; their use in connection with treatment of bone disorders, such as conditions mediated by osteoclasts (e.g., increased osteoclast activity) and/or characterised by (e.g., increased) bone resorption, such as osteoporosis (e.g., osteoporosis not associated with inflammation; e.g., osteoporosis associated with a genetic predisposition, sex hormone deficiency, or ageing), cancer associated bone disease, and Paget's disease of bone. Data supplied from the esp@cenet database - Worldwide

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(54) Title: CANNABINOID RECEPTOR INVERSE AGONISTS AND NEUTRAL ANTAGONISTS AS THERAPEUTIC AGENTS FOR THE TREATMENT OF BONE DISORDERS

(57) Abstract: The present invention pertains to cannabinoid (CB) receptor inverse agonists and neutral antagonists, and especially CB1 and CB2 inverse agonists and neutral antagonists; such as, for example, certain pyrazole compounds; their use in the inhibition of osteoclasts (for example, the inhibition of the survival, formation, and/or activity of osteoclasts), and/or in the inhibition of bone resorption; their use in connection with treatment of bone disorders, such as conditions mediated by osteoclasts (e.g., increased osteoclast activity) and/or characterised by (e.g., increased) bone resorption, such as osteoporosis (e.g., osteoporosis not associated with inflammation; e.g., osteoporosis associated with a genetic predisposition, sex hormone deficiency, or ageing), cancer associated bone disease, and Paget's disease of bone.

CANNABINOID RECEPTOR INVERSE AGONISTS AND NEUTRAL ANTAGONISTS AS THERAPEUTIC AGENTS FOR THE TREATMENT OF BONE DISORDERS

RELATED APPLICATIONS

This application is related to: United Kingdom patent application GB 0305343.6 filed 07 March 2003; United Kingdom patent application GB 0317241.8 filed 23 July 2003; and United Kingdom patent application GB 0324283.1 filed 16 October 2003; the contents of each of which are incorporated herein by reference in their entirety.

TECHNICAL FIELD

The present invention pertains to cannabinoid (CB) receptor inverse agonists and neutral antagonists, and especially CB1 and CB2 inverse agonists and neutral antagonists; such as, for example, certain pyrazole compounds; their use in the inhibition of osteoclasts (for example, the inhibition of the survival, formation, and/or activity of osteoclasts), and/or in the inhibition of bone resorption; their use in connection with treatment of bone disorders, such as conditions mediated by osteoclasts (e.g., increased osteoclast activity) and/or characterised by (e.g., increased) bone resorption, such as osteoporosis (e.g., osteoporosis not associated with inflammation; e.g., osteoporosis associated with a genetic predisposition, sex hormone deficiency, or ageing), cancer associated bone disease, and Paget's disease of bone.

BACKGROUND

Throughout this specification, including any claims which follow, unless the context requires otherwise, the word "comprise," and variations such as "comprises" and "comprising," will be understood to imply the inclusion of a stated integer or step or group of integers or steps, but not the exclusion of any other integer or step or group of integers or steps.

It must be noted that, as used in the specification and any appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a pharmaceutical carrier" includes mixtures of two or more such carriers, and the like.

Ranges are often expressed herein as from "about" one particular value, and/or to "about" another particular value. When such a range is expressed, another embodiment includes from the one particular value and/or to the other particular value. Similarly, when values

are expressed as approximations, by the use of the antecedent "about," it will be understood that the particular value forms another embodiment.

Functions of Bone

The function of bone is to provide mechanical support for joints, tendons and ligaments, to protect vital organs from damage and to act as a reservoir for calcium and phosphate in the preservation of normal mineral homeostasis. Diseases of bone compromise these functions, leading to clinical problems such as bone pain, bone deformity, fracture and abnormalities of calcium and phosphate homeostasis.

Types of Bone

The normal skeleton contains two types of bone; cortical or compact bone, which makes up most of shafts (diaphysis) of the long bones such as the femur and tibia, and trabecular or spongy bone which makes up most of the vertebral bodies and the ends of the long bones.

Trabecular bone has a greater surface area than cortical bone and because of this is remodeled more rapidly. This means that conditions associated with increased bone turnover tend to affect trabecular bone more quickly and more profoundly than cortical bone. Cortical bone is arranged in so-called Haversian systems which consists of a series of concentric lamellae of collagen fibres surrounding a central canal that contains blood vessels. Nutrients reach the central parts of the bone by an interconnecting system of canaliculi that run between osteocytes buried deep within bone matrix and lining cells on the bone surface. Trabecular bone has a similar structure, but here the lamellae run in parallel to the bone surface, rather than concentrically as in cortical bone.

Bone Composition

The organic component of bone matrix comprises mainly of type I collagen; a fibrillar protein formed from three protein chains, wound together in a triple helix. Collagen type I is laid down by bone forming cells (osteoblasts) in organised parallel sheets (lamellae) and subsequently the collagen chains become cross-linked by specialised covalent bonds which help to give bone its tensile strength. When bone is formed rapidly (for example in Paget's disease, or in bone metastases), the lamellae are laid down in a disorderly fashion giving rise to "woven bone", which is mechanically weak and easily fractured. Bone matrix also contains small amounts of other collagens and several non-collagenous proteins and glycoproteins. Some of these, such as osteocalcin, are specific to bone,

whereas others, such as osteopontin and fibronectin and various peptide growth factors are also found in other connective tissues. The function of non-collagenous bone proteins is unclear, but it is thought that they are involved in mediating the attachment of bone cells to bone matrix, and in regulating bone cell activity during the process of bone remodelling. The organic component of bone forms a framework upon which mineralisation occurs. During bone formation, osteoblasts lay down uncalcified bone matrix (osteoid) which contains the components described above and small amounts of other proteins, which are adsorbed from extracellular fluid. After a lag phase of about 10 days, the matrix becomes mineralised, as hydroxyapatite ($(Ca_{10}(PO_4)_6(OH)_2)$ crystals are deposited in the spaces between collagen fibrils. Mineralisation confers upon bone the property of mechanical rigidity, which complements the tensile strength, and elasticity derived from bone collagen.

Bone cell function and bone remodelling

The mechanical integrity of the skeleton is maintained by the process of bone remodelling, which occurs throughout life, in order that damaged bone can be replaced by new bone. Remodelling can be divided into four phases; resorption; reversal, formation and quiescence (see, e.g., Raisz, 1988; Mundy, 1996). At any one time approximately 10% of bone surface in the adult skeleton is undergoing active remodeled whereas the remaining 90% is quiescent.

Osteoclast Formation and Differentiation

Remodelling commences with attraction of bone resorbing cells (osteoclasts) to the site, which is to be resorbed. These are multinucleated phagocytic cells, rich in the enzyme tartrate-resistant acid phosphatase, which are formed by fusion of precursors derived from the cells of monocyte/macrophage lineage. Recent work has identified several molecules that are of key importance in the regulation of osteoclast differentiation (see, e.g., Ralston, 1997). The transcription factor *PU-1* which is expressed in early osteoclast precursors is necessary for the initial stages of osteoclast and monocyte differentiation, whereas other transcription factors including *c-fos* and *NFkB* play an essential role in stimulating differentiation of committed precursors to mature osteoclasts. Osteoclast formation and activation is also dependent on close contact between osteoclast precursors and bone marrow stromal cells. Stromal cells secrete the cytokine *M-CSF* (macrophage colony stimulating factor), which is essential for differentiation of both osteoclasts and macrophages from a common precursor. Stromal cells also express a molecule called *RANK ligand (RANKL)* on the cell surface, which interacts with another cell surface receptor present on osteoclast precursors called *RANK* (Receptor Activator of Nuclear

Factor Kappa B) to promote differentiation of osteoclast precursors to mature osteoclasts. The *RANK-RANKL* interaction is blocked by another molecule called Osteoprotegerin (*OPG*), which is a "decoy" ligand for RANK and which acts a potent inhibitor of osteoclast formation (see, e.g., Kong et al., 1999; Yasuda et al., 1998). Recent work suggests that many of the factors that promote osteoclast formation and bone resorption do so by regulating expression of these molecules.

Mature osteoclasts form a tight seal over the bone surface and resorb bone by secreting hydrochloric acid and proteolytic enzymes through the "ruffled border" into a space beneath the osteoclast (Howship's lacuna). Formation of this ruffled border is critically dependent on the presence of *c-src*, a cell membrane associated signalling protein. The hydrochloric acid secreted by osteoclasts dissolves hydroxyapatite and allows proteolytic enzymes (mainly Cathepsin K and matrix metalloproteinases) to degrade collagen and other matrix proteins. Molecules which have been identified as being important in regulating osteoclast activity include; carbonic anhydrase II (Ca-II) which catalyses formation of hydrogen ions within osteoclasts; TCIRG1, which encodes a subunit of the osteoclast proton pump, and Cathepsin K which degrades collagen and other non-collagenous proteins. Deficiency of these proteins causes osteopetrosis which is a disease associated with increased bone density and osteoclast dysfunction. After resorption is completed osteoclasts undergo programmed cell death (apoptosis), in the so-called reversal phase which heralds the start of bone formation. It has recently been discovered that many of the drugs, which are used clinically to inhibit bone resorption, such as bisphosphonates and oestrogen do so by promoting osteoclast apoptosis (see, e.g., Hughes et al., 1997).

Osteoblast Formation and Differentiation

Bone formation begins with attraction of osteoblast precursors, which are derived from mesenchymal stem cells in the bone marrow, to the bone surface. Although these cells have the potential to differentiate into many cell types including adipocytes, myocytes, and chondrocytes it is now known that the key trigger for osteoblast differentiation is expression of a regulatory molecule called Cbfa1 in pre-osteoblasts (see, e.g., Rodan et al., 1997). Cbfa1 is a transcription factor that activates co-ordinated expression of genes characteristic of the osteoblast phenotype such as osteocalcin, type I collagen and alkaline phosphatase. In contrast, expression of the transcription factor PPAR gamma promotes the cells towards adipocyte differentiation. It is currently thought that some cases of osteoporosis may occur because there is an imbalance between the rate of osteoblast and adipocyte differentiation in bone. Mature osteoblasts are plump cuboidal cells, which are responsible for the production of bone matrix. They are rich in the

enzyme alkaline phosphatase and the protein osteocalcin, which are used clinically as serum markers of osteoblast activity. Osteoblasts lay down bone matrix which is initially unmineralised (osteoid), but which subsequently becomes calcified after about 10 days to form mature bone. During bone formation, some osteoblasts become trapped within the matrix and differentiate into osteocytes, whereas others differentiate into flattened "lining cells" which cover the bone surface. Osteocytes connect with one another and with lining cells on the bone surface by an intricate network of cytoplasmic processes, running through cannaliculi in bone matrix. Osteocytes appear to act as sensors of mechanical strain in the skeleton, and release signalling molecules such as prostaglandins and nitric oxide (NO), which modulate the function of neighbouring bone cells.

Bone remodelling is a highly organised process, but the mechanisms which determine where and when remodelling occurs are poorly understood. Mechanical stimuli and areas of micro-damage are likely to be important in determining the sites at which remodelling occurs in the normal skeleton. Increased bone remodelling may result from local or systemic release of inflammatory cytokines like interleukin-1 and tumour necrosis factor in inflammatory diseases. Calciotropic hormones such as parathyroid hormone (PTH) and 1,25-dihydroxyvitamin D, act together to increase bone remodelling on a systemic basis allowing skeletal calcium to be mobilised for maintenance of plasma calcium homeostasis. Bone remodelling is also increased by other hormones such as thyroid hormone and growth hormone, but suppressed by oestrogen, androgens and calcitonin.

Common Bone Diseases

Osteoporosis is a common disease characterised by reduced bone density, deterioration of bone tissue and increase risk of fracture. Many factors contribute to the pathogenesis of osteoporosis including poor diet, lack of exercise, smoking and excessive alcohol intake. Osteoporosis may also arise in association with inflammatory diseases such as rheumatoid arthritis, endocrine diseases such as thyrotoxicosis and with certain drug treatments such as glucocorticoids. However one of the most important factors in the pathogenesis of osteoporosis is heredity.

Paget's disease of bone is a common condition of unknown cause, characterised by increased bone turnover and disorganised bone remodeling, with areas of increased osteoclastic and osteoblast activity. Although Pagetic bone is often denser than normal, the abnormal architecture causes the bone to be mechanically weak, resulting in bone deformity and increased susceptibility to pathological fracture.

Bone involvement is a feature of many types of cancer (see, e.g., Guise & Mundy, 1998). Cancer-associated bone disease can be manifest by the occurrence of hypercalcaemia or the development of osteolytic and/or ostesclerotic metastases. Increased osteoclastic bone resorption plays a key role in the pathogenesis of both conditions. Whilst almost any cancer can be complicated by bone metastases, the most common causes are multiple myeloma, breast carcinoma, and prostate carcinoma. The most common tumours associated with hypercalcaemia are multiple myeloma, breast carcinoma, and lung carcinoma.

Known Methods of Treatment

Accelerated osteoclastic bone resorption plays an key role in the pathogenesis of common bone diseases such as osteoporosis, Paget's disease of bone, cancer-associated bone disease and periarticular bone loss in inflammatory disease states such as rheumatoid arthritis (see, e.g., Rodan et al., 2000). Because of this, most drugs which are used for the prevention and treatment of these diseases have inhibitory effects on osteoclast differentiation and/or function.

At present the most commonly used types of drugs used to suppress osteoclast activity in these diseases are bisphophonates (BPs).

Bisphosphonates (previously known as diphosphonates) are an important class of drugs used in the treatment of bone diseases involving excessive bone destruction or resorption. Bisphosphonates are structural analogues of naturally occurring pyrophosphate. Whereas pyrophosphate consists of two phosphate groups linked by an oxygen atom (P-O-P), bisphosphonates have two phosphate groups linked by a carbon atom (P-C-P). This makes bisphosphonates very stable and resistant to degradation. Furthermore, like pyrophosphate, bisphosphonates have very high affinity for calcium and therefore target to bone mineral *in vivo*. The carbon atom that links the two phosphate groups has two side chains attached to it, which can be altered in structure. This gives rise to a multitude of bisphosphonate compounds with different anti-resorptive potencies.

Bisphosphonates such as etidronate, clodronate, tiludronate, alendronate, risedronate, and zoledronate are highly effective agents for the treatment of osteoporosis, Paget's disease and cancer-associated bone disease. These agents can be divided into two broad classes depending on their mechanism of action.

Simple bisphosphonates such as etidronate, clodronate and tiludronate target to bone mineral and are taken up by resorbing osteoclasts. These drugs then become

incorporated into non-hydrolysable analogues of adenosine triphosphate (ATP) and these metabolites inhibit osteoclast activity by interfering with essential metabolic functions (see, e.g., Frith et al., 2001; Rogers et al., 1999).

Amino bisphosphonates are also taken up by resorbing osteoclasts where they inhibit the farnesyl synthase enzyme (FPP synthase) (see, e.g., Dunford et al., 2001). This is responsible for lipid modification (prenylation) of small GTP binding proteins such as Ras, Rac, cdc42 and Rho that play a critical role in osteoclast function (see, e.g., Rogers et al., 1999). In the absence of prenylation, these signaling proteins are unable to target properly to the plasma membrane causing impairment of osteoclast function (see, e.g., Coxon et al., 2000).

Calcitonin has also been successfully used in the treatment of bone diseases such as hypercalcaemia of malignancy and osteoporosis (see, e.g., Chesnut et al., 2000; Chambers et al., 1982). Calcitonin exerts a direct inhibitory effect on bone resorption by interacting with the G-protein coupled calcitonin receptor which is highly expressed on mature osteoclasts.

Hormone replacement therapy with oestrogen is highly effective in preventing postmenopausal bone loss, but has not been studied in other diseases associated with increased osteoclastic bone resorption such as Paget's disease, hypercalcaemia and metastatic bone disease. The mechanism by which oestrogen inhibits bone resorption is incompletely understood, but it is believed to involve inhibition of expression of bone-resorbing cytokines such as IL-1, TNF and IL-6 and modulation of Osteoprotegerin and RANK ligand production within the bone microenvironment (see, e.g., Pacifici, 1996). Related compounds which act on the oestrogen receptor such as raloxifene and tibolone have similarly been used in the prevention and treatment of post-menopausal bone loss, but are not thought to be effective in treating osteoclastic bone resorption in other conditions.

Inhibitors of p38 MAP kinases have been suggested to have possible utility as inhibitors of bone resorption based on their inhibitory effects on cytokine production (see, e.g., Weier et al.). The effect of these agents on bone resorption has not been studied however and, in any case, the role of p38 MAP kinase activation in the pathogenesis of increased bone resorption in common bone diseases such as osteoporosis, Paget's disease, cancer associated bone disease and inflammation induced bone disease has not been established.

Whilst all of the above treatments are effective, each has specific drawbacks. Gastrointestinal intolerance is a problem with amino bisphosphonates and intestinal absorption of all bisphosphonates is poor. There is also a concern that long-term accumulation of bisphosphonates may occur in the skeleton, leading to impaired healing of microfractures and decreased bone quality. Calcitonin is less effective than the bisphosphonates, has to be given parenterally and has a relatively short duration of action. Hormone replacement therapy, raloxifene and tibolone are effective for the treatment of post-menopausal bone loss and osteoporosis, but not for the treatment of other bone diseases.

In view of this, there remains a clinical need for new drugs for the treatment of bone disorders which offer, for example, one or more the following benefits:
(a) improved activity;
(b) improved efficacy;
(c) improved specificity;
(d) reduced toxicity (e.g., cytotoxicity);
(e) complement the activity of other treatments (e.g., chemotherapeutic agents);
(f) reduced intensity of undesired side-effects;
(g) fewer undesired side-effects;
(h) simpler methods of administration (e.g., route, timing, compliance);
(i) reduction in required dosage amounts;
(j) reduction in required frequency of administration;
(k) increased ease of synthesis, purification, handling, storage, etc.;
(l) reduced cost of synthesis, purification, handling, storage, etc.

New Treatments

In the search for new treatments for bone disease, attention has traditionally focussed on metabolic pathways and receptor systems which affect cellular function in the bone microenvironment.

Recent studies have shown, however, that the central nervous system also plays an important role in the regulation of bone mass. For example, mice with leptin deficiency have increased bone mass which can be reversed by intracerebral infusion of low concentrations of leptin (see, e.g., Ducy et al., 2000).

The inventors realized that bone mass may be influenced by the neural pathways. This is supported by recent work that identified the neuropeptide Y2 receptor as one component of a hypothalamic relay which regulates bone mass (see, e.g., Baldock et al., 2002).

The inventors have determined that certain ligands of the endocannabinoid system (specifically, cannabinoid receptor inverse agonists and neutral antagonists) play a role in regulating osteoclast activity and bone mass, and hence are of value in the prevention and treatment of bone disorders, including those mediated by osteoclasts (e.g., increased osteoclast activity) and/or characterised by (e.g., increased) bone resorption.

Cannabinoid receptor modulators have been investigated as a possible treatment for some of the symptoms of multiple sclerosis, including spasticity and neuropathic pain; in the prevention and treatment of nausea and vomiting associated with chemotherapy; and in the treatment of anorexia associated with wasting diseases.

Localisation of CB2 receptors on cells of the immune system has led to the suggestion that cannabinoid receptor ligands may be of value as immunosuppressive and anti-inflammatory agents. Studies in animal models have shown that both CB2 selective agonists (see, e.g., Hanus et al., 1999) and CB1 selective agonists (see, e.g., Clayton et al., 2002; Smith et al., 2001) have anti-inflammatory effects. These anti-inflammatory effects are blocked by CB2 selective inverse agonists (Hanus et al, 1999; Conti et al., 2002) and by CB1 selective inverse agonists (Clayton et al., 2002) respectively.

Some publications have asserted that certain cannabinoid receptor ligands are useful in the treatment of inflammatory and autoimmune diseases; however, these documents do not refer to osteoporosis. See, for example: Inaba et al., 2003, which describes 2-oxoquinoline compounds as peripheral type cannabinoid immunomodulators; Barth et al., 1999, which describes certain 3-pyrazolecarboxamide derivatives having cannabinoid receptor affinity as potent immunomodulators; Barth et al., 2002b, which describes certain pyrazolecarboxylic acid derivatives for the treatment of obesity; Martin et al., 2003a which describes pyrazole cannabinoid agonist and antagonists.

Osteoporosis is a well-known complication of inflammatory diseases including rheumatoid arthritis, ankylosing spondylitis and inflammatory bowel disease (see, e.g., Sambrook et al., 1988; Compston et al., 1994; Croucher et al., 1993; Will et al., 1989). However, most instances of osteoporosis occurring in clinical practice are unrelated to inflammatory diseases and are instead associated with a genetic predisposition, sex hormone deficiency, or ageing. Furthermore, many of the drugs used to treat inflammatory and autoimmune diseases, such as steroids and NSAIDS, are a cause of osteoporosis, and so are contra-indicated.

Some publications have asserted, usually without any supporting evidence or data, that certain cannabinoid receptor agonists are useful in the treatment of inflammatory and autoimmune diseases including osteoporosis or bone disease which occurs as a complication of an inflammatory disease. See, for example: Barth et al., 2002a, which describes certain 3-arylindoles as CB2 receptor agonists; Bender et al., 1998, which describes pyrazoles as CB2 receptor agonists for the treatment of immune disorders, inflammation and osteoporosis; Bender et al., 1999, which describes adamantyl phenols as cannabinoid receptor agonists in the treatment of immunologically-mediated inflammatory diseases; Kozlowski et al., 2002, which describes compounds capable of stimulating cannabinoid CB2 receptors to treat conditions characterised by inflammation immunomodulatory irregularities; Mittendorf et al., 1999, which describes agonists of the CB1 and CB2 receptor for the treatment of autoimmunologically related diseases of the bone.

These documents do not mention bone diseases associated with abnormalities of bone turnover such as Paget's disease or metastatic bone disease, or those associated with sex hormone deficiency or ageing. Furthermore, nowhere in these documents is there any teaching or suggestion that the cannabinoid receptor ligands have modulatory effects on bone formation or bone resorption, or that they might be useful in the treatment of osteoporosis which is *not* associated with inflammatory disease, or in the treatment of other bone diseases. It is generally recognized that such modulatory effects (either inhibition of bone resorption or stimulation of bone formation) are required for the treatment of osteoporosis and other diseases characterised by abnormalities of bone remodelling such as Paget's disease and cancer-associated bone disease.

Chackalamanil et al., 2001, and Xiang et al., 1998, assert that certain compounds, which allegedly are CB2 receptor modulators (e.g., antagonists and agonists) may have value in the treatment of inflammatory diseases and therefore be useful in the treatment of osteoporosis. No biological data is provided: instead, a prophetic assay and anticipated results are described. Xiang et al., 1998, also asserts, without any supporting evidence, that the compounds modulate bone formation/resorption (see page 12, lines 21-24 therein). Note that the "hypothesis" of both of these patents (that cannabinoid CB2 receptor *antagonists* would be of value in the treatment of various inflammatory conditions and associated osteoporosis) is contradicted by the teaching of many other documents (see, e.g., Bender et al., 1999, where it is asserted that cannabinoid CB2 receptor *agonists* would be of value in the treatment of the same range of conditions). Thus, in the absence of any supporting data, the "hypothesis" of both of these patents would not be seriously considered by the skilled worker.

At best, the above publications might suggest that cannabinoid receptor *agonists* might possess the desired activity, and even then, only in the context of osteoporosis associated with inflammatory diseases. None of these publications demonstrate that cannabinoid (e.g., CB1 or CB2) receptor *inverse agonists* or *neutral antagonists* have the desired therapeutic utility. Certainly none of the publications teach or suggest that cannabinoid (e.g., CB1 or CB2) receptor *inverse agonists* or *neutral antagonists* modulate osteoclast or osteoblast function, or might be useful in the treatment of osteoporosis not associated with inflammation, or in the treatment of other bone diseases.

SUMMARY OF THE INVENTION

One aspect of the present invention pertains to use of a cannabinoid receptor inverse agonist or a cannabinoid receptor neutral antagonist for the manufacture of a medicament for the treatment of a bone disorder.

Another aspect of the present invention pertains to use of a cannabinoid receptor *inverse agonist* for the manufacture of a medicament for the treatment of a bone disorder

Another aspect of the present invention pertains to use of a cannabinoid receptor *neutral antagonist* for the manufacture of a medicament for the treatment of a bone disorder

One aspect of the present invention pertains to a method of treating a bone disorder comprising administering to a patient in need of treatment thereof a therapeutically effective amount of a cannabinoid receptor inverse agonist or a cannabinoid receptor neutral antagonist.

Another aspect of the present invention pertains to a method of treating a bone disorder comprising administering to a patient in need of treatment thereof a therapeutically effective amount of a cannabinoid receptor *inverse agonist.*

Another aspect of the present invention pertains to a method of treating a bone disorder comprising administering to a patient in need of treatment thereof a therapeutically effective amount of a cannabinoid receptor *neutral antagonist.*

One aspect of the present invention pertains to use of a compound for the manufacture of a medicament for the treatment of a bone disorder, wherein said compound is selected from compounds having a chemical formula as described herein.

One aspect of the present invention pertains to a method of treating a bone disorder comprising administering to a patient in need of treatment thereof a therapeutically effective amount of a compound selected from compounds having a chemical formula as described herein.

In one embodiment, the bone disorder is osteoporosis (e.g., osteoporosis not associated with inflammation; e.g., osteoporosis associated with a genetic predisposition, sex hormone deficiency, or ageing), cancer associated bone disease, or Paget's disease of bone.

In one embodiment, the bone disorder is: osteoporosis which is not associated with inflammation; cancer associated bone disease; or Paget's disease of bone.

In one embodiment, the bone disorder is: osteoporosis associated with a genetic predisposition, sex hormone deficiency, or ageing.

One aspect of the invention pertains to use of compounds as described herein (e.g., certain pyrazoles, etc.) for the manufacture of a medicament for the treatment of a bone disorder.

Another aspect of the present invention pertains to a method of treating a bone disorder comprising administering to a patient in need of treatment thereof a therapeutically effective amount of a compound as described herein (e.g., certain pyrazoles, etc.).

As will be appreciated by one of skill in the art, features and preferred embodiments of one aspect of the invention will also pertain to other aspects of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a graph showing J774 survival (% control) versus concentration of drug, for compounds AM630 (■) and AM251 (□) after 72 hours, by Alamar Blue assay (n=3).

Figure 2 is a bar-graph of TRAcP MNC for control, AM251 (at 10 μM) ($p<0.03$), and AM251 (at 20 μM) ($p<0.01$).

Figure 3 is a bar-graph of resorbed area for control, AM251 (at 10 μM) ($p<0.03$), and AM251 (at 20 μM) ($p<0.01$).

Figure 4 is a graph of TRAcP MNC versus concentration of AM251 (■) and SR144528 ("SR144") (Δ) (n=3).

Figure 5 is a graph of resorbed area versus concentration of AM251 (■) and SR144528 ("SR144") (Δ) (n=3).

Figure 6 is a graph of Alamar Blue J774 murine macrophage survival (% control) versus concentration of drug, for compounds AM251 (■), SR144528 ("SR144") (Δ) and JTE-907 ("JTE") (●) (n=3).

Figure 7 is a graph of osteoblast survival (% control) versus concentration of drug, for compounds SR144528 ("SR144") (Δ), AM251 (■) and JTE-907 ("JTE") (●) (n=3).

Figure 8 is a graph of Alamar Blue J774 murine macrophage survival (% control) versus concentration of drug, for three analogs of SR144528: "methyl" (♦), "piperidinyl" (■) (n=3), and "benzodioxo" (Δ).

Figure 9 is a bar graph showing percent changes in trabecular density, for: (a) Sham operation, no drug; (b) Sham operation, AM251 (6 mg/kg); (c) OVX operation, no drug; and (d) OVX operation, AM251 (6 mg/kg).

Figure 10 is a bar graph showing percent changes in trabecular density, for: (a) Sham operation, no drug; (b) Sham operation, SR144528 ("SR144") (6 mg/kg); (c) OVX operation, no drug; and (d) OVX operation, SR144528 ("SR144") (6 mg/kg).

Figure 11 is a bar graph showing percent changes in femoral bone mineral content, for: (a) Sham operation, no drug; (b) Sham operation, SR144528 ("SR144") (6 mg/kg); (c) OVX operation, no drug; and (d) OVX operation, SR144528 ("SR144") (6 mg/kg) as measured by dual energy x-ray absorptiometry.

Figure 12 is a bar graph showing percent changes in femoral bone mineral density for (a) Sham operation, no drug; (b) Sham operation, SR144528 ("SR144") (6 mg/kg); (c) OVX operation, no drug; and (d) OVX operation, SR144528 ("SR144") (6 mg/kg) as measured by dual energy x-ray absorptiometry.

DETAILED DESCRIPTION

One aspect of the present invention pertains to the use of cannabinoid receptor inverse agonists and cannabinoid receptor neutral antagonists, in the inhibition of osteoclasts (for

example, the inhibition of the survival, formation, and/or activity of osteoclasts), and/or in the inhibition of bone resorption; and in connection with treatment of bone disorders, such as conditions mediated by osteoclasts (e.g., increased osteoclast activity) and/or characterised by (e.g., increased) bone resorption.

Cannabis and Cannabinoids

The plant species *Cannabis sativa L.*, also known as cannabis, marijuana, and Indian hemp, is of the genus *Cannabis L.* (hemp) and the family *Cannabaceae* (also *Cannabidaceae*) (hemp family). Two sub-species are known, *ssp. indica* and *ssp. sativa*, as well as several varieties of the latter (e.g., *Purple Haze*).

Cannabis is a source of fiber (hemp), oil, medicines, and narcotics (psychotropics). Most varieties contain biologically active terpenoid derivatives, such as cannabinol, isomeric tetrahydrocannabinols, and cannabidiol, collectively referred to as "cannabinoids." A variety of derivatives and analogs of these compounds have been prepared and studied. Both the natural product Δ^9-THC (also known as Dronabinol® and Marinol®) and the synthetic analogue Cesamet® (also known as Nabilone®) are licensed for use in the United Kingdom as antiemetics. See, for example, Goutopoulos et al., 2002.

Cannabinoid Binding Sites

Specific cannabinoid binding sites for exogenous cannabinoids were first demonstrated in 1988. Since then, two distinct cannabinoid binding site receptors have been identified: the CB1 receptor and the CB2 receptor. CB1 is a ubiquitous receptor found in the central nervous system (CNS) and the periphery, and in both neural and non-neural tissues. The CB2 receptor has a more limited distribution, principally in cells associated with the immune system. Recently, another cannabinoid receptor has been characterised in the brain which binds anandamide and SR141716A, but not other cannabinoid receptor ligands (see, e.g., Breivogel et al., 2001). In addition, SR144528 may interact with a CB2-like receptor located on immune cells (Pertree and Ross, 2002).

The endogenous cannabinoid (endocannabinoid) system comprises at least two receptors (CB1 and CB2), each with different localisations and functions; a family of endogenous ligands; and a specific molecular machinery for the synthesis, transport, and inactivation of these ligands. This system has been shown to have a huge range of effects in the nervous, immune and cardiovascular systems (see, e.g., Lichtman et al., 2002; Parolaro et al., 2002; Rice et al., 2002).

The existence of the CB1 and CB2 binding sites strongly suggested the existence of one or more endogenous ligands (endogenous cannabinoids, endocannabinoids) that exert their physiological activity upon binding to these receptors.

In 1992, the first endogenous ligand (endogenous cannabinoid, endocannabinoid), arachidonyl ethanolamide (AEA), also known as anandamide, which binds to CB1, was isolated from human brain tissue. Subsequently, a number of endogenous cannabinoids (e.g., such as those shown below) have been identified and shown to be involved in the control of various physiological functions including pain transmission, inflammation, appetite, motor function, learning and memory (see, e.g., Pertwee et al., 2002).

Cannabinoid receptor modulators are currently being investigated as a possible treatment for some of the symptoms of multiple sclerosis, neuropathic and inflammatory pain, the prevention and treatment of nausea and vomiting associated with chemotherapy and the treatment of anorexia associated with wasting diseases.

Localisation of CB2 receptors on cells of the immune system has led to the suggestion that cannabinoid agonists may also play a role as immunosuppressive and anti-inflammatory agents. In fact, CB2 receptors have been implicated in the anti-inflammatory actions of endocananbinoids and a CB2-selective agonist has been shown to be a potent anti-inflammatory compound (see, e.g., Hanus et al., 1999).

Using DNA microarray technology it has recently been shown that, activation of CB2 receptors in promyelocytic cells (HL-60) induces an up-regulation of 5 genes involved in cytokine production and regulation (IL-8, MCP-1, MIP-1β, TNFα, A20) and 4 genes involved in transcription and cell cycling (Jun B, Aldose C, BTG2, IκB-α) (Derocq et al, 2000). These changes are highly sensitive to cannabinoids, since significant alterations in gene expression are induced by low concentrations of agonist (10 nM). The transcriptional events reported are implicated in the cell differentiation program and suggest that CB2 receptors are important in control of the initialisation of cell maturation. Furthermore, CB2 receptor activation appears to induce conditions that promote the transition of HL-60 cells to a more monocytic/granulocytic phenotype. In addition to the observed agonist-induced enhancement of mRNA expression, a decrease in the basal levels mRNA expression was observed in the presence of the inverse agonist SR144528.

Despite the pleiotropic effects of cannabinoids, there have been no prior suggestions or data to support the hypothesis that the endocannabinoid system may play a role in bone metabolism.

Cannabinoid Receptor Inverse Agonists and Neutral Antagonists

Thus, one aspect of the present invention pertains to use of a cannabinoid receptor inverse agonist or a cannabinoid receptor neutral antagonist for the manufacture of a medicament for the treatment of a bone disorder.

Another aspect of the present invention pertains to a method of treating a bone disorder comprising administering to a patient in need of treatment thereof a therapeutically effective amount of a cannabinoid receptor inverse agonist or a cannabinoid receptor neutral antagonist.

In one embodiment, the cannabinoid receptor is CB1.
In one embodiment, the cannabinoid receptor is CB2.
In one embodiment, the cannabinoid receptor is CB1 or CB2.

In one embodiment, the cannabinoid receptor inverse agonist or cannabinoid receptor neutral antagonist is a CB1 inverse agonist or a CB1 neutral antagonist.

In one embodiment, the cannabinoid receptor inverse agonist or cannabinoid receptor neutral antagonist is a CB2 inverse agonist or a CB2 neutral antagonist.

In one embodiment, the cannabinoid receptor inverse agonist or cannabinoid receptor neutral antagonist is a CB1 inverse agonist or a CB1 neutral antagonist or a CB2 inverse agonist or a CB2 neutral antagonist.

In one embodiment, the cannabinoid receptor inverse agonist or cannabinoid receptor neutral antagonist is a CB1 inverse agonist or a CB1 neutral antagonist; *and* is also a CB2 inverse agonist or a CB2 neutral antagonist.

In one embodiment, the cannabinoid receptor inverse agonist or cannabinoid receptor neutral antagonist is a CB1 inverse agonist or a CB1 neutral antagonist; *but is not* a CB2 inverse agonist or a CB2 neutral antagonist.

In one embodiment, the cannabinoid receptor inverse agonist or cannabinoid receptor neutral antagonist is a CB2 inverse agonist or a CB2 neutral antagonist; *but is not* a CB1 inverse agonist or a CB1 neutral antagonist.

Thus, one aspect of the present invention pertains to use of a cannabinoid receptor *inverse agonist* for the manufacture of a medicament for the treatment of a bone disorder

Another aspect of the present invention pertains to a method of treating a bone disorder comprising administering to a patient in need of treatment thereof a therapeutically effective amount of a cannabinoid receptor *inverse agonist*.

In one embodiment, the cannabinoid receptor inverse agonist is a CB1 inverse agonist.

In one embodiment, the cannabinoid receptor inverse agonist is a CB2 inverse agonist.

In one embodiment, the cannabinoid receptor inverse agonist is a CB1 inverse agonist or a CB2 inverse agonist.

In one embodiment, the cannabinoid receptor inverse agonist is a CB1 inverse agonist; *and* is also a CB2 inverse agonist or a CB2 neutral antagonist.

In one embodiment, the cannabinoid receptor inverse agonist is a CB2 inverse agonist; *and* is also a CB1 inverse agonist or a CB1 neutral antagonist.

In one embodiment, the cannabinoid receptor inverse agonist is a CB1 inverse agonist; *but is not* a CB2 inverse agonist or a CB2 neutral antagonist.

In one embodiment, the cannabinoid receptor inverse agonist is a CB2 inverse agonist; *but is not* a CB1 inverse agonist or a CB1 neutral antagonist.

Thus, one aspect of the present invention pertains to use of a cannabinoid receptor *neutral antagonist* for the manufacture of a medicament for the treatment of a bone disorder

Another aspect of the present invention pertains to a method of treating a bone disorder comprising administering to a patient in need of treatment thereof a therapeutically effective amount of a cannabinoid receptor *neutral antagonist*.

In one embodiment, the cannabinoid receptor neutral antagonist is a CB1 neutral antagonist.

In one embodiment, the cannabinoid receptor neutral antagonist is a CB2 neutral antagonist.

In one embodiment, the cannabinoid receptor neutral antagonist is a CB1 neutral antagonist or a CB2 neutral antagonist.

In one embodiment, the cannabinoid receptor neutral antagonist is a CB1 neutral antagonist; *and* is also a CB2 inverse agonist or a CB2 neutral antagonist.

In one embodiment, the cannabinoid receptor neutral antagonist is a CB2 neutral antagonist; *and* is also a CB1 inverse agonist or a CB1 neutral antagonist.

In one embodiment, the cannabinoid receptor neutral antagonist is a CB1 neutral antagonist; *but is not* a CB2 inverse agonist or a CB2 neutral antagonist.

In one embodiment, the cannabinoid receptor neutral antagonist is a CB2 neutral antagonist; *but is not* a CB1 inverse agonist or a CB1 neutral antagonist.

In one embodiment, the cannabinoid receptor inverse agonist or cannabinoid receptor neutral antagonist is (additionally) CB1 selective.

In one embodiment, the cannabinoid receptor inverse agonist or cannabinoid receptor neutral antagonist is (additionally) CB2 selective.

Cannabinoid (CB) Receptor Ligands - Affinity

In general, a particular ligand which binds to a particular receptor is said to have affinity for that receptor.

A measure of affinity is often determined using a binding assay, for example, a competition or displacement assay, in which a candidate ligand competes with, or displaces, a known (or reference) ligand with a known (or reference) affinity. Such assays yield an inhibition constant (Ki) for the candidate ligand. The Ki value is inversely proportional to the affinity of the candidate ligand for the receptor. Thus, a low Ki value signifies a high affinity. In general, a Ki value of 10 μM (10,000 nM) or less is considered to be a meaningful affinity for the receptor, and indicates that the candidate compounds is in fact a ligand for that receptor.

Assays for determining cannabinoid receptor affinity are well known. See, for example, Ross et al., 1999a; Ross et al., 1999b; Huffman et al., 2000; Huffman et al., 2001. For example, radio-ligand displacement assays using tissues that contain the CB1 receptor (brain, CB1 transfected cell lines) or the CB2 receptor (spleen, CB2 transfected cell lines)

are common. Examples of suitable radio-labelled known (reference) ligands include tritium-labeled SR141716A (a CB1-specific receptor inverse agonist), tritium-labeled CP55940 (a CB1/CB2 receptor agonist). One suitable method is described below.

In one embodiment, the cannabinoid receptor inverse agonist or cannabinoid receptor neutral antagonist has a cannabinoid receptor inhibition constant (Ki) of 10 μM or less.

In one embodiment, range is: 1 μM or less; 500 nM or less; 100 nM or less; 50 nM or less; 25 nM or less; 10 nM or less; 5 nM or less; 2 nM or less; or 1 nM or less.

In one embodiment, the range is: from 0.001 nM to 10 μM; from 0.001 nM to 1 μM; from 0.001 nM to 500 nM; from 0.001 nM to 100 nM; from 0.001 nM to 50 nM; from 0.001 nM to 25 nM; from 0.001 nM to 10 nM; from 0.001 nM to 5 nM; from 0.001 nM to 2 nM; or from 0.001 nM to 1 nM.

In one embodiment, the cannabinoid receptor inverse agonist or cannabinoid receptor neutral antagonist has a CB1 inhibition constant (Ki) as defined above.

In one embodiment, the cannabinoid receptor inverse agonist or cannabinoid receptor neutral antagonist has a CB2 inhibition constant (Ki) as defined above.

In one embodiment, the a cannabinoid receptor inverse agonist or a cannabinoid receptor neutral antagonist has a CB1 inhibition constant (Ki) as defined above, *and* a CB2 inhibition constant (Ki) as defined above.

Cannabinoid Receptor Binding Assays

Cannabinoid receptor binding (and thus ligand affinity) can readily be determined by looking for displacement of a suitable known ligand by a test ligand from mouse brain and spleen membranes. Examples of suitable known ligands include tritium labeled SR141716A (a CB1-specific receptor inverse agonist) and CP55940 (a CB1/CB2 receptor agonist).

One suitable method is described next. MF1 mice are killed by cervical dislocation and the desired tissues (brain and spleen) dissected out and placed into cold centrifugation buffer (320 mM sucrose, 2mM Tris EDTA, 5 mM $MgCl_2$) on ice. Tissue is then homogenized with an ultra-turrax polytron homogeniser. The homogenate is centrifuged at 1600 x g for 10 minutes, the supernatant saved on ice and the pellet re-suspended in cold centrifugation buffer and centrifuged at 1600 x g for 10 minutes. The supernatants

are combined and centrifuged at 32000 x g for 20 minutes. This supernatant is discarded and the pellet resuspended in 50 mL of Tris Buffer (50 mM Tris , 2 mM EDTA and 5 mM $MgCl_2$), incubated at 37°C for 10 minutes and centrifuged at 23000 x g for 20 minutes. The final pellet is resuspended in 40 mL Tris Buffer and left to stand at room temperature for 40 minutes. This solution is then centrifuged at 11000 x g for 15 minutes and the pellet resuspended in assay buffer (1 mM $MgCl_2$, 50 mM Tris, 1 mM EDTA) to a concentration of 1 mg/mL as determined by the Lowry method (Bio-Rad Dc kit).

Radioligand binding assays are performed, for example, with the CB1 receptor inverse agonist [^{3}H]SR141716A (0.5nM) (brain membranes) or [^{3}H]CP55940 (0.5 nM) (spleen membranes) in assay buffer containing 1 mg/mL BSA, the total assay volume being 500 µL. Binding is initiated by the addition of membranes (100 µg). The vehicle concentration of 0.1% DMSO is kept constant throughout. Assays are carried out at 37°C for 60 minutes before termination by addition of ice-cold wash buffer (50 mM Tris buffer, 1 mg/mL BSA) and vacuum filtration using a 12-well sampling manifold (Brandel Cell Harvester) and Whatman GF/B glass-fibre filters that had been soaked in wash buffer at 4°C for 24 hours. Each reaction tube is washed five times with a 4 mL aliquot of buffer. The filters are oven-dried for 60 minutes and then placed in 5 mL of scintillation fluid (Ultima Gold XR, Packard), and radioactivity quantitated by liquid scintillation spectrometry.

Specific binding is defined as the difference between the binding that occurred in the presence and absence of 1 µM unlabelled ligand and reported as a percentage of the total radio-ligand bound in brain and spleen respectively.

The concentrations of competing ligands (test compounds) to produce 50% displacement of the radioligand (IC50) from specific binding sites is calculated, for example, using GraphPad Prism (GraphPad Software, San Diego). Inhibition constant (Ki) values are calculated using the equation of Cheng & Prusoff (see, e.g., Cheng et al., 1973).

Cannabinoid (CB) Receptor Ligands - Functional Characteristics (1)

Although binding studies measure the affinity of a ligand for the receptor, such studies do not indicate the functional characteristics of the ligand (that is, whether it acts as an agonist, neutral antagonist, inverse agonist, etc.).

Thus, many cannabinoid receptor ligands may also be conveniently classified according to their functional characteristics, for example, their effect upon cannabinoid receptor activity, for example, as an agonist, neutral antagonist, inverse agonist, etc.

Both CB1 and CB2 receptors belong to the G protein-coupled receptor (GPCR) super-family and are coupled to inhibition of adenylyl cyclase and activation of extracellular signal-regulated cascade (ERK). See, e.g., the review by Pertwee, 2001.

The traditional model of G protein-coupled receptor (GPCR) action is based on the premise that the binding of an agonist to the receptor is necessary for receptor activation. However, it is now clear that some receptor activation occurs spontaneously, without agonist binding, the receptors being "constitutively active."

Cannabinoid CB1 and CB2 receptors appear to be constitutively active. A large body of evidence for this has been obtained from high expression recombinant cell lines where cannabinoid receptor inverse agonists stimulate adenylyl cyclase and inhibit ERK (see, e.g., Bouaboula et al., 1996; Bouaboula et al., 1997; Bouaboula et al., 1999). By sequestration of Gi proteins, cannabinoid inverse agonists not only inhibit constituitively active CB1/CB2 receptors but also inhibit receptor activation by other unrelated Gi-dependent receptors (see, e.g., Bouaboula et al., 1999).

In general, ligands that do not bind directly to a receptor, but do affect the receptor's function, may be described as "modulators." There are numerous examples of so-called allosteric modulators of G-protein coupled receptors that bind to a site closely related to the receptor and modulate the function of the receptor (see, e.g., Vaulquelin et al., 2002). Such sites may exist for the cannabinoid receptors; however, none have yet been identified.

Thus, many cannabinoid receptor ligands may be further classified as:

(a) cannabinoid receptor *agonists*, which activate the receptor; partial agonists also activate the receptor, but with lower efficacy than a full agonist;

(b) cannabinoid receptor *inverse agonists*, which both block the action of the agonist and attenuate receptor-constitutive activity;

(c) cannabinoid receptor *neutral antagonists*, which block the action of the agonist but are ineffective on the receptor-constitutive activity; they may also be low efficacy partial agonists that behave as antagonists.

Examples of (a) cannabinoid receptor agonists include, but are not limited to:
L-759633, which is a CB2 selective agonist (see, e.g., Gareau et al., 1996; Ross et al., 1999a);
L-759666, which is a CB2 selective agonist (see, e.g., Gareau et al., 1996; Ross et al., 1999a);

JWH-133, which is a CB2 selective agonist (see, e.g., Huffman et al., 2001);
HU308, which is a CB2 selective agonist (see, e.g., Hanus et al., 1999).
Δ^9-THC, which has considerably lower efficacy at the CB2 receptor than CB1, and has been reported to behave as a CB2 receptor antagonist (see, e.g., Bouaboula et al., 1999);
O-1238, which is a non-selective partial agonist (see, e.g., Ross et al., 1999b).
Anandamide, which is a partial agonist at the CB2 receptor (see Pertwee, 1999).

Examples of (b) cannabinoid receptor inverse agonists include, but are not limited to:
SR141716A, which is CB1 selective (see, e.g., Bouaboula et al., 1997);
AM281, which is CB1 selective (see, e.g., Gifford et al., 1997; Lan et al., 1999);
AM251, which is CB1 selective (see, e.g., Lan et al., 1999);
LY321035, which is CB1 selective (see, e.g., Felder et al., 1998);
SR144528, which is CB2 selective (see, e.g., MacLennan et al., 1998);
JTE-907, which is CB2 selective (see, e.g., Iwamura et al., 2001);
O-1184 which has equal affinity for CB1 and CB2 receptors but is a CB2 receptor inverse agonist (see, e.g., Ross et al., 1999b).

Examples of candidates for (c) cannabinoid receptor neutral antagonists include, but are not limited to:
cannabinol, which is a CB1 receptor antagonist (see, e.g., MacLennan et al., 1998);
Δ^9-THC, which has considerably lower efficacy at the CB2 receptor than CB1, and has been reported to behave as a CB2 receptor antagonist (see, e.g., Bouaboula et al., 1999);
O-1238, a non-selective partial agonist (see, e.g., Ross et al., 1999b).

Some examples of cannabinoid receptor agonists, neutral antagonists, and partial agonists are listed in Table 1.

Table 1

Compounds that display partial agonist, neutral antagonist and inverse agonist activity at CB1 or CB2 receptors.

	Ki (nM)		Classification	
Ligand	CB1	CB2	CB1	CB2
SR141716A	12.3	702	Inverse agonist	Inverse agonist
LY320135	141	14900	Inverse agonist	Inactive
AM281	12	4200	Inverse agonist	Status unclear
AM251	0.5	2000	Inverse agonist	Status unclear
SR144528	437	5.6	Inverse agonist	Inverse agonist
AM630	5152	31.2	Inverse agonist	Inverse agonist
JTE-907	684	1.55	Inactive	Inverse agonist
O1184	5.2	7.4	Partial agonist	Inverse agonist
O1238	3.5	7.8	Partial agonist	Partial agonist
Cannabinol	115	580	Neutral antagonist	Inverse agonist
Δ^9THC	41	36	Partial agonist	Neutral antagonist
Anandamide	89	371	Agonist	Partial agonist

While the compounds in the above Table have been extensively characterised, many more compounds with affinity for CB1 and CB2 receptors have been less well characterised. While radioligand binding experiments have confirmed that such compounds have selectivity for either the CB1 or CB2 receptor, some have not yet been classified as being agonists, neutral antagonists, inverse agonists, etc.

Cannabinoid (CB) Receptor Ligands - Functional Characteristics (2)

Cannabinoid receptor ligands may be functionally characterised, for example, according to:

(1) their effect upon adenylyl cylase activity; and/or

(2) their effect upon [^{35}S]-γ-GTP binding.

Thus, many cannabinoid receptor ligands may be further classified as:

(A) cannabinoid receptor agonists, which:

(i) inhibit adenylyl cyclase activity.

Inhibition of adenylyl cyclase is measured using a cyclic AMP assay (see below). Certain compounds will cause formation of cyclic AMP (i.e., stimulate cyclic AMP production) in cells and tissues. One such compound is forskolin. The stimulation of cyclic AMP production by forskolin is inhibited by cannabinoid receptor agonists. The cyclic AMP assay will yield an IC50 (see methods) for cannabinoid receptor agonists. The level of inhibition of forskolin-stimulated cyclic AMP production is expressed as a percent (%) of the cyclic AMP production induced by forskolin alone. The concentration of cannabinoid receptor ligand which produces 50% inhibition (IC50) of forskolin-stimulated cyclic AMP production is calculated using GraphPad Prism (GraphPad Software, San Diego). If a cannabinoid receptor ligand has an IC50 value for inhibition of forskolin-stimulated cyclic AMP production of from 0.001 nM to 10 μM, then it is considered to be a cannabinoid receptor AGONIST.

(ii) stimulate [^{35}S]-γ-GTP binding.

Agonist activation of a G-protein coupled receptor by a compound causes GTP to attach to the receptor. In this assay, the GTP is radiolabelled ([^{35}S]-γ-GTP) and thus the amount of GTP linked to the receptor can be measured. The amount of GTP binding to the receptor is directly proportional to the level of activation of the receptor. The [^{35}S]-γ-GTP binding assay measures the amount of radioactivity bound to cells and tissues. The assay will yield an EC50 value for cannabinoid receptor agonists (see methods). The [^{35}S]-γ-GTP bound in the presence of a cannabinoid receptor agonist will increase and is expressed as a percent (%) of the specific binding. The % stimulation at each concentration of agonist is calculated and a concentration-response curve drawn using Prism (GraphPad). The concentration of agonist producing 50% stimulation of [^{35}S]-γ-GTP binding is defined as the EC50. The Emax value is the maximum response to a given agonist. If a cannabinoid receptor ligand has an EC50 value of from 0.001 nM to 10 μM for stimulation of [^{35}S]-γ-GTP binding, then it is considered to be an AGONIST.

or:

(B) cannabinoid receptor inverse agonists, which:

(i) stimulate adenylyl cylase activity.

Inhibition of adenylyl cyclase is measured using a cyclic AMP assay (see below). Certain compounds will cause formation of cyclic AMP (i.e., stimulate cyclic AMP production) in cells and tissues. One such compound is forskolin. The stimulation of cyclic AMP production by forskolin is enhanced by cannabinoid receptor inverse agonists.

Cannabinoid receptor inverse agonists will also stimulate the production of cyclic AMP in the absence of forskolin. A cannabinoid receptor inverse agonist will enhance forskolin-stimulated cyclic AMP production. A graph of this enhancement is drawn using GraphPad Prism (GraphPad Software, San Diego) and the EC50 is the concentration of cannabinoid receptor ligand that produces a 50% stimulatory response. If a cannabinoid receptor ligand has an EC50 value for stimulation of cyclic AMP production of from 0.001 nM to 10 μM, then it is considered to be a cannabinoid receptor INVERSE AGONIST.

(ii) inhibit [^{35}S]-γ-GTP binding.

Inverse agonist activation of a G-protein coupled receptor by a compound causes GTP to detach from the receptor. In this assay, the GTP is radiolabeled ([^{35}S]-γ-GTP) and thus the amount of GTP linked to the receptor can be measured. The [^{35}S]-γ-GTP binding assay measures the amount of radioactivity bound to cells and tissues. The assay will yield an IC50 value for cannabinoid receptor inverse agonists (see methods). The % inhibition is calculated for each concentration of compound and calculated and a concentration-response curve drawn using Prism (GraphPad). The concentration of inverse agonist producing 50% inhibition of [^{35}S]-□-GTP binding is defined as the IC_{50}. If a cannabinoid receptor ligand has an IC50 value of from 0.001 nM to 10 μM for inhibition of [^{35}S]-γ-GTP binding, then it is considered to be an INVERSE AGONIST.

or:

(C) cannabinoid receptor neutral antagonists, which:

(i) block the inhibition of adenylyl cylase activity by cannabinoid receptor agonists.

As described in (A) above, the stimulation of cyclic AMP production by forskolin is inhibited by cannabinoid receptor agonist. The cyclic AMP assay will yield an IC50 (see methods) for cannabinoid receptor agonists. A neutral antagonist will have no effect upon cyclic AMP production when added to cells or tissues alone. A neutral antagonist will block the inhibition of cyclic AMP production observed with an agonist (as described in (A) above). A neutral antagonist will cause the IC50 for an agonist to be increased. The ratio of the IC50 value in the presence and absence of an antagonist is referred to as the "dose ratio" (DR). The following formula is used to calculate the Kb value for the antagonist, where B is the concentration of antagonist: (DR - 1) = (B)(Kb). The Kb value is a measure of the ability of the compound to antagonise the activation of the receptor by the agonist. A cannabinoid receptor ligand with a Kb value of from 0.001 nM to 10 μM would be considered to be an antagonist. Note that both inverse agonists and antagonists will

block the effect of agonists, but a neutral antagonist will NOT stimulate the production of cyclic AMP.

(ii) block the stimulation of [^{35}S]-γ-GTP binding by a cannabinoid receptor agonist.

A neutral antagonist interacting with a G-protein coupled receptor will have no effect upon the GTP bound to the receptor. In this assay, the GTP is radiolabelled ([^{35}S]-γ-GTP) and thus the amount of GTP linked to the receptor can be measured. The [^{35}S]-γ-GTP binding assay measures the amount of radioactivity bound to cells and tissues. A neutral antagonist will block the stimulation of [^{35}S]-γ-GTP binding observed with an agonist (as described in (A) above). A neutral antagonist will cause the EC50 for an agonist to be increased. The ratio of the EC50 value in the absence and presence of an antagonist is referred to as the "dose ratio" (DR). The following formula is used to calculate the Kb value for the antagonist, where B is the concentration of antagonist: (DR - 1) = (B)(Kb). The Kb value is a measure of the ability of the compound to antagonise the activation of the receptor by the agonist. A cannabinoid receptor ligand with a Kb value of from 0.001 nM to 10 μM would be considered to be an antagonist. Note that both inverse agonists and antagonists will block the effect of agonists, but a neutral antagonist will NOT inhibit [^{35}S]-γ-GTP binding.

Thus:

In one embodiment, the cannabinoid receptor inverse agonist stimulates cyclic AMP production with an EC50 value of 10 μM or less.

In one embodiment, the cannabinoid receptor inverse agonist inhibits [^{35}S]-γ-GTP binding with an IC50 value of 10 μM or less.

In one embodiment, both of the above apply.

In one embodiment, the cannabinoid receptor neutral antagonist does not affect cyclic AMP production, but blocks the inhibition of cyclic AMP production by a cannabinoid receptor agonist with a Kb value of 10 μM or less.

In one embodiment, the cannabinoid receptor neutral antagonist does not affect the binding of [^{35}S]-γ-GTP, but does block the stimulation of [^{35}S]-γ-GTP binding by an agonist with a Kb value of 10 μM or less.

In one embodiment, both of the above apply.

In one embodiment, range is: 1 μM or less; 500 nM or less; 100 nM or less; 50 nM or less; 25 nM or less; 10 nM or less; 5 nM or less; 2 nM or less; or 1 nM or less.

In one embodiment, the range is: from 0.001 nM to 10 μM; from 0.001 nM to 1 μM; from 0.001 nM to 500 nM; from 0.001 nM to 100 nM; from 0.001 nM to 50 nM; from 0.001 nM to 25 nM; from 0.001 nM to 10 nM; from 0.001 nM to 5 nM; from 0.001 nM to 2 nM; or from 0.001 nM to 1 nM.

Cyclic AMP Assay

Cannabinoid receptors CB1 and CB2 are coupled to inhibition of adenylyl cyclase (see, e.g., Bidault-Russell et al., 1990; Childers et al., 1996). Adenylyl cyclase is an enzyme that catalyses the production of cyclic adenosine monophosphate (AMP). Thus, activation of the receptor leads to the inhibition of the production of cyclic AMP. Certain compounds, such as forskolin, stimulate adenylyl cyclase. Accumulation of cyclic AMP is then measured using a radio-immunoassay, and is indicative of adenylyl cyclase activation. The radioimmunoassay uses radiolabelled cyclic AMP. The amount of radioactivity can be measured and will be proportional to the level of cyclic AMP that is produced. The cyclic AMP assay is performed with a phosphodiesterase inhibitor present. This is necessary because phosphodiesterase is an enzyme that rapidly breaks down cyclic AMP. An example of a phosphodiesterase inhibitor is rolipram. The cyclic AMP assay is performed using cells that contain CB1 receptors only or cells that contain CB2 receptors only (Chinese Hamster Ovary Cells or Human Embryonic Kidney Cells, respectively). The cyclic AMP assay may also be also performed with tissues that contain CB1 receptors (e.g., brain) or CB2 receptors (e.g., spleen).

The cells or tissues are incubated for 30 minutes at 37°C with the cannabinoid receptor ligand and the phosphodiesterase inhibitor rolipram (Sigma) (50 μM) in phosphate buffered saline (PBS) containing 1 mg/ml bovine serum albumin (Sigma). The cells or tissues are then incubated for a further 30 minutes incubation with 2 μM forskolin (Sigma). The reaction is terminated by addition 0.1 M hydrochloric acid and the mixture is centrifuged in a microfuge to remove cell debris. The resulting pellet contains cell debris and the supernatant contains the [^{3}H] cyclic AMP. A sample of a supernatant is removed and the pH is adjusted to pH 8-9 using 1 M NaOH. The cyclic AMP content is then measured using a radioimmunoassay kit ([^{3}H] Biotrack assay TRK432, from Amersham Biosciences), following the manufacturers instructions. The amount of radioactivity in each sample is counted using a Beckman scintillation counter. The amount is cyclic AMP in each sample is calculated from the level of radioactivity.

[^{35}S]-γ-GTP Assay

Activation of a G-protein coupled receptor by an agonist leads to the replacement of guanosine diphosphate (GDP) with guanosine triphosphate (GTP). The level of binding of GTP to the receptor is proportional to the level of receptor activation. The level of binding is measured by using a radiolabelled from of GTP called [^{35}S]-γ-GTP. Thus the radioactivity can be measured and is proportional to the amount of GTP bound to the receptor. The [^{35}S]-γ-GTP binding assay is performed with cells that contain CB1 receptors only or cells that contain CB2 receptors only (Chinese Hamster Ovary cells or human embryonic kidney cells, respectively). The [^{35}S]-γ-GTP binding assay may also be performed with tissues that contain CB1 receptors (e.g., brain) or CB2 receptors (e.g., spleen).

Cells (see above) that contain CB1 or CB2 receptors only are removed from flasks by scraping, and are re-suspended in homogenisation buffer (0.32 M sucrose / 50 mM Tris), and homogenised using an Ultra-Turrex homogeniser. If tissues are used, the homogenate is prepared as for a radioligand binding assay (see above). The homogenate is diluted with Tris buffer (50 mM, pH 7.4) and centrifuged at 50,000 x g for 45 minutes. Cell membranes (20 µg) (see above) are incubated in assay buffer containing 2 mg/ml fatty acid free bovine serum albumin (BSA), 20 µM GDP, and 0.1 nM [^{35}S]-γ-GTP (New England Nuclear). The assay buffer contains: 50 mM Tris; 10 mM $MgCl_2$; 100 mM NaCl; 0.2 mM EDTA at pH 7.4. Incubation times are for 90 minutes at 30°C. The reaction is terminated by the addition of 4 mL of ice-cold wash buffer (50 mM Tris, 1 mg/mL BSA, pH 7.4) followed by rapid filtration under vacuum through Whatman GF/B glass fibre filters using a 12-tube Brandel cell harvester. The filters are washed 3 times with 4 mL of wash buffer. The filters are then dried, placed in scintillation fluid, and bound radioactivity is determined by liquid scintillation counting and reported, e.g., in units of disintegrations per minute (dpm). The binding of [^{35}S]-γ-GTP is determined (a) in the presence of 20 µM GDP (this is the "total binding", TB), and (b) in the presence of 10 µM S-γ-GTP (this is the "non-specific binding", NSB). The level of binding of [^{35}S]-γ-GTP is reported as a percentage change with respect to basal levels. The "specific" binding (SB) of [^{35}S]-γ-GTP to the receptor is defined as the total binding less the non-specific binding (i.e., SB=TB-NSB), and this value is taken as 100%.

Cannabinoid (CB) Receptor Ligands - Chemical Structure

Cannabinoid receptor ligands may also be conveniently classified according to chemical structure, for example, as discussed below.

Many of these classes, and their members, are also cannabinoid receptor inverse agonists or cannabinoid neutral antagonists, as described herein, and are suitable for use in the present invention.

Thus, one aspect of the invention pertains to use of such compounds for the manufacture of a medicament for the treatment of a bone disorder.

Another aspect of the present invention pertains to a method of treating a bone disorder comprising administering to a patient in need of treatment thereof a therapeutically effective amount of such compounds.

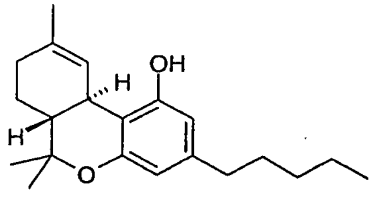
A. Classical Cannabinoids

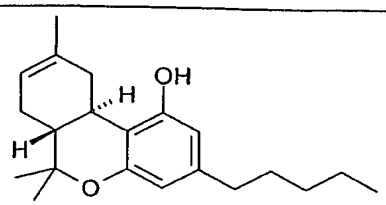
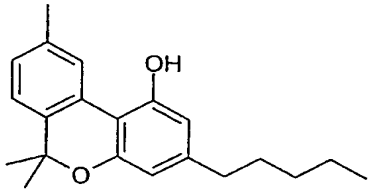
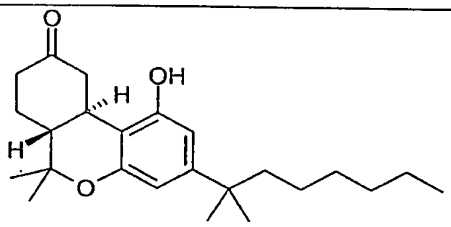
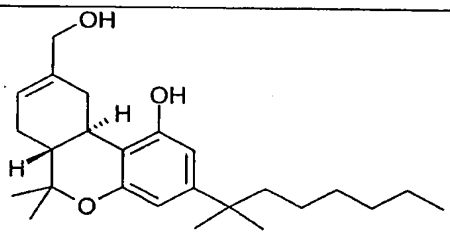
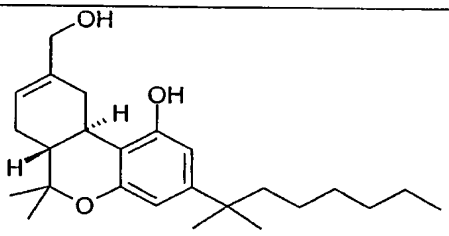
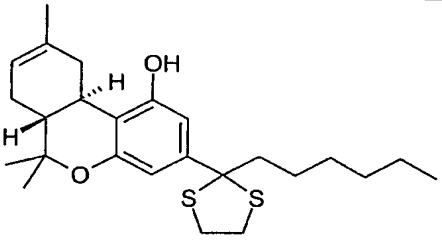
This class of ligands includes those which are structurally similar to Δ^9-THC and have a (partially hydrogenated) 10a*H*-benzo[c]chromene core.

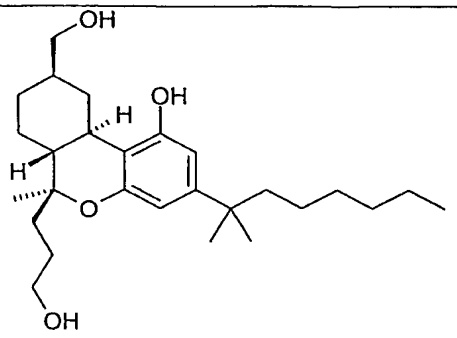
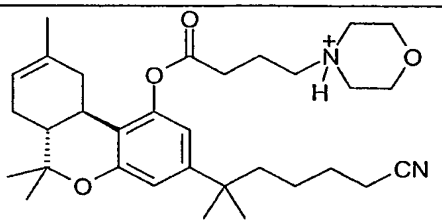
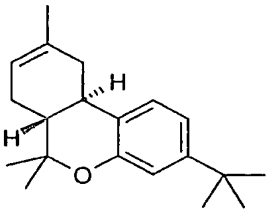
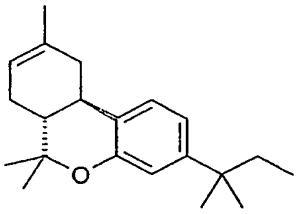
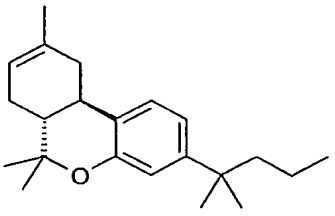
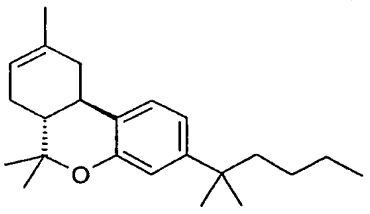
Thus, one aspect of the invention pertains to use of a compound (e.g., a cannabinoid receptor inverse agonist or a cannabinoid receptor neutral antagonist) for the manufacture of a medicament for the treatment of a bone disorder, wherein the compound is Δ^9-THC or an analogue or derivative thereof.

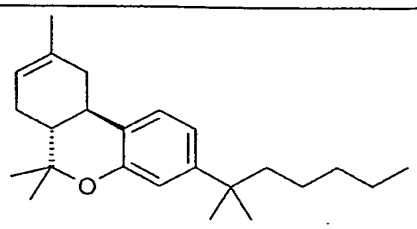
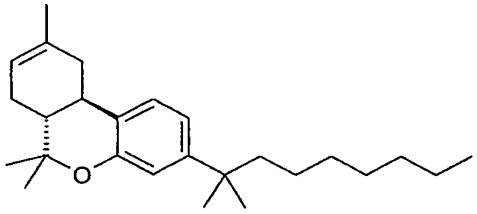
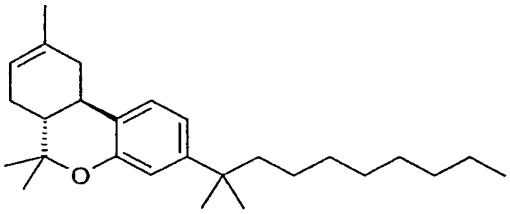
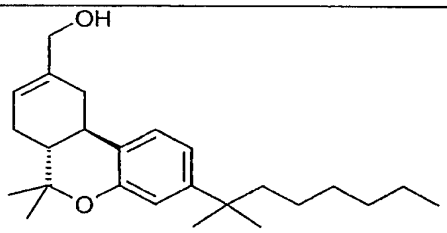
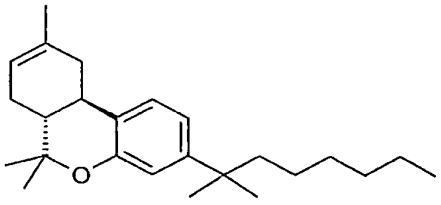
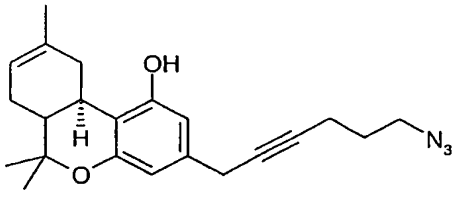
Another aspect of the present invention pertains to a method of treating a bone disorder comprising administering to a patient in need of treatment thereof a therapeutically effective amount of a compound (e.g., a cannabinoid receptor inverse agonist or a cannabinoid receptor neutral antagonist) that is Δ^9-THC or an analogue or derivative thereof.

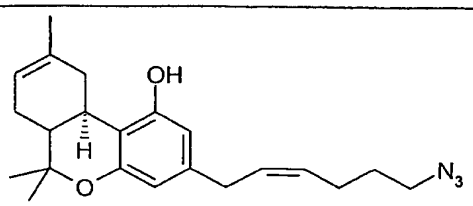
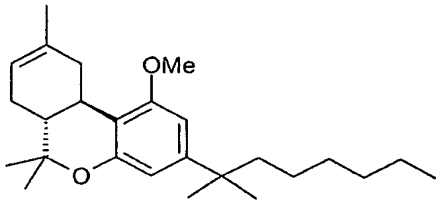
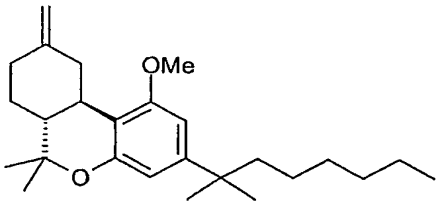
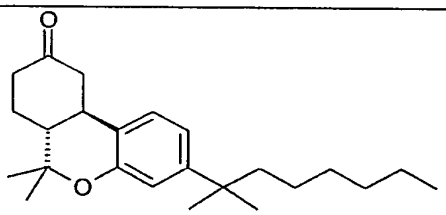
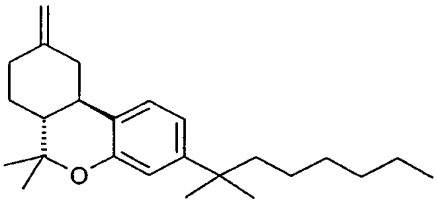
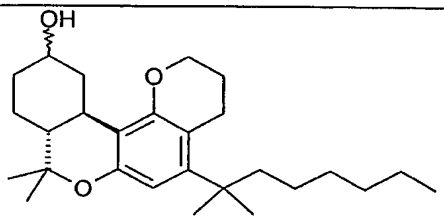
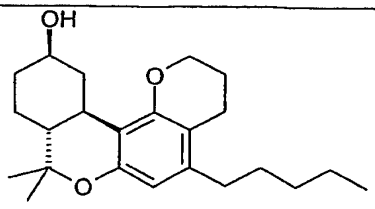
Examples of such compounds include, but are not limited to, the following:

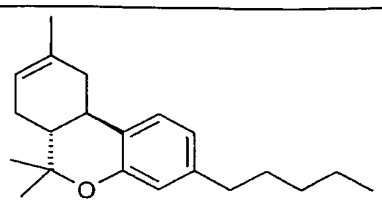
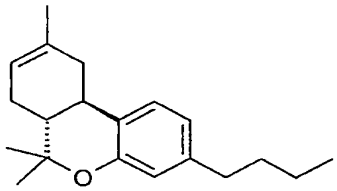
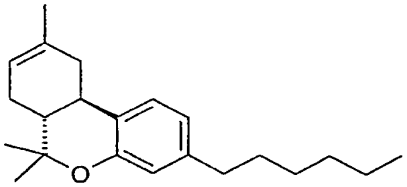
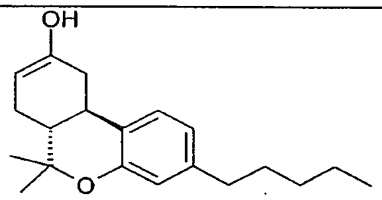
Compound	Structure
Δ^9-tetrahydrocannabinol (Δ^9-THC) = Δ^1-3,4-trans-isomer (Δ^1-THC)	

Compound	Structure
Δ^8-tetrahydrocannabinol (Δ^8-THC) = Δ^6-3,4-trans-isomer (Δ^6-THC)	
cannabinol	
Cesamet (Nabilone)	
HU-210	
dehydroxy-HU-210	
AMG-3	

Compound	Structure
AM-919	
O-1057	
JWH-140	
JWH-139	
JWH-133	
JWH-065	

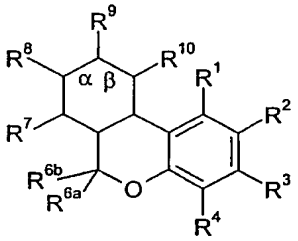
Compound	Structure
JWH-066	
JWH-067	
JWH-068	
JWH-051	
JWH-057	
O-1184	

Compound	Structure
O-1238	
L759633	
L759656	
JWH-101	
JWH-104	
JWH-102 & JWH-104	
O,2-Propano-9β-11-nor-HHC	

Compound	Structure
JWH-056	
JWH-132	
JWH-125	
JWH-075	

See, for example: Gareau et al., 1996; Huffman et al., 1999; Huffman, 2000; Pertwee et al., 2001; Goutopoulos et al., 2002; Khanolkar et al., 2001. Many more analogs are known in the art.

In one embodiment, the compound (e.g., the cannabinoid receptor inverse agonist or the cannabinoid receptor neutral antagonist) is selected from compounds of the following formula:



(1)

wherein:

α is a single bond, and β is a double bond; or:

α is a double bond, and β is a single bond; or:

α is a single bond, and β is a single bond;
R^1 is independently -H, -OH, an ether group, or an ester group;
R^3 is independently C_{1-12}alkyl or substituted C_{1-12}alkyl;
each of R^{6a} and R^{6b} is independently -H, C_{1-4}alkyl, or substituted C_{1-4}alkyl;
R^9 is independently -H, C_{1-4}alkyl, or substituted C_{1-4}alkyl;
when α is a single bond, and β is a single bond: then R^9 may additionally be $=CH_2$ or =O;
each of R^2, R^4, R^7, R^8, and R^{10} is independently -H, -OH, halo, C_{1-4}alkyl, or C_{1-4}alkoxy;
and stereoisomers thereof;
and pharmaceutically acceptable salts, solvates, amides, esters, ethers, chemically protected forms, and prodrugs thereof.

In one embodiment, α is a single bond, and β is a double bond.
In one embodiment, α is a double bond, and β is a single bond.
In one embodiment, α is a single bond, and β is a single bond.

In one embodiment, R^1 is independently -H, -OH, C_{1-7}alkoxy, C_{1-7}alkyl-acyloxy.
In one embodiment, R^1 is independently -H, -OH, -OMe, -OEt, -OC(=O)Me, -O(C=O)Et.
In one embodiment, R^1 is independently -H or -OH.
In one embodiment, R^1 is independently -OH.
In one embodiment, R^1 is independently -H.

In one embodiment, R^3 is independently C_{4-12}alkyl or substituted C_{4-12}alkyl.
Examples of substituents include hydroxy, halo, azido, cyano, thioalkyl.
In one embodiment, R^3 is independently C_{4-12}alkyl.
In one embodiment, R^3 is independently linear or branched C_{4-12}alkyl.
In one embodiment, R^3 is independently branched C_{4-12}alkyl.
In one embodiment, R^3 is independently $-C(CH_3)_2(CH_2)_nCH_3$, wherein n is 0, 1, 2, 3, 4, 5, 6, or 7.

In one embodiment, each of R^{6a} and R^{6b} is independently -H, C_{1-4}alkyl or hydroxy-C_{1-4}alkyl.
In one embodiment, each of R^{6a} and R^{6b} is independently C_{1-4}alkyl.
In one embodiment, each of R^{6a} and R^{6b} is independently -Me.

In one embodiment, R^9 is independently -H, C_{1-4}alkyl, or hydroxy-C_{1-4}alkyl; or when α is a single bond, and β is a single bond: then R^9 is -H, C_{1-4}alkyl, hydroxy-C_{1-4}alkyl, $=CH_2$ or =O.
In one embodiment, R^9 is independently -H, Me, $-CH_2OH$; or when α is a single bond, and β is a single bond: then R^9 is independently -H, Me, $-CH_2OH$, $=CH_2$ or =O.
In one embodiment, R^9 is independently -H, -Me, or $-CH_2OH$.

In one embodiment, each of R^2, R^4, R^7, R^8, and R^{10} is independently -H, -OH, -Me, or -OMe.

In one embodiment, each of R^2, R^4, R^7, R^8, and R^{10} is independently -H or -OH.

In one embodiment, each of R^2, R^4, R^7, R^8, and R^{10} is independently -H.

In one embodiment, the compound has a stereoisomeric structure corresponding to that of Δ^9-THC.

For groups which are indicated to be "substituted" or "optionally substituted," certain preferred substituents are described below under the heading "Some Preferred Substituents."

In one embodiment, the compound is as structurally defined above, and additionally has one or more of the functional characteristics defined herein (e.g., has a particular cannabinoid receptor inhibition constant (Ki); is a cannabinoid receptor inverse agonist; is a cannabinoid receptor neutral antagonist; is a CB2 inverse agonist; etc.).

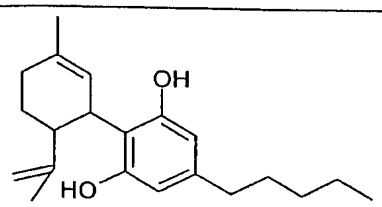
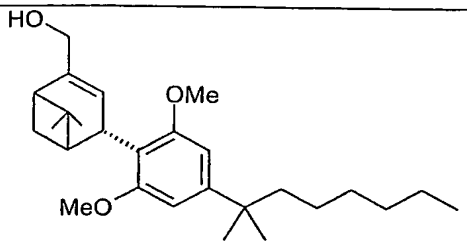
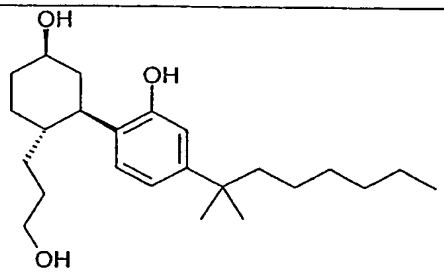
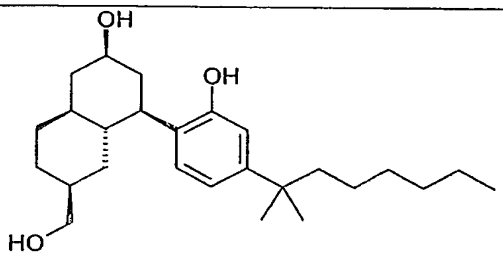
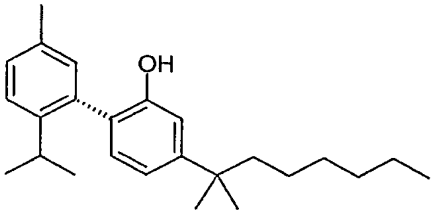
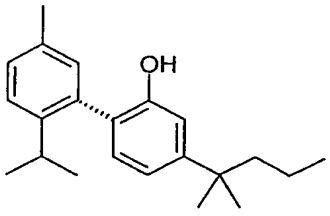
B. Non-Classical Cannabinoids

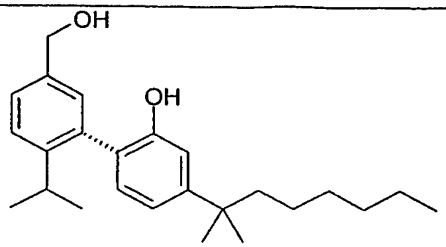
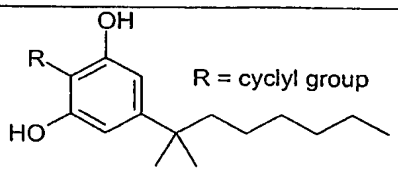
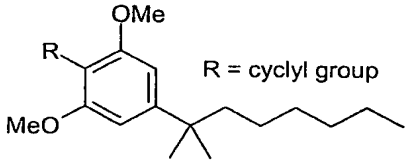
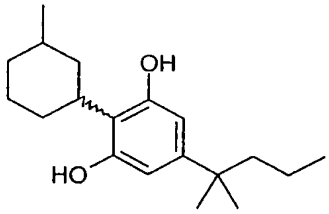
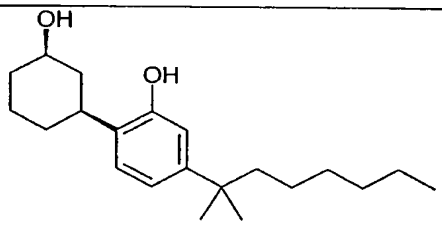
This class of ligands includes those which are structurally similar to Δ^9-THC but which, for example, lack the oxygen atom of the 10a*H*-benzo[c]chromene core.

Thus, one aspect of the invention pertains to use of a compound (e.g., a cannabinoid receptor inverse agonist or a cannabinoid receptor neutral antagonist) for the manufacture of a medicament for the treatment of a bone disorder, wherein the compound is cannabidiol or an analogue or derivative thereof.

Another aspect of the present invention pertains to a method of treating a bone disorder comprising administering to a patient in need of treatment thereof a therapeutically effective amount of a compound (e.g., a cannabinoid receptor inverse agonist or a cannabinoid receptor neutral antagonist) that is cannabidiol or an analogue or derivative thereof.

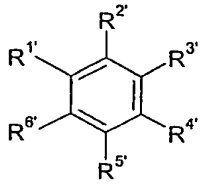
Examples of such compounds include, but are not limited to, the following:

Compound	Structure
cannabidiol	
HU-308	
CP-55940	
CP-55244	
O-1376	
O-1532	

Compound	Structure
O-1601	
O-1424; O-1422; O-1656; O-1160; O-1425; O-1661; O-1662; O-1423; O-1658; O-1659; O-1663; O-1657; O-1797A; O-1798B; O-1826; O-1871	
O-1999; O-1964; O-1965; O-1962; O-2092; O-2122; O-2122; O-2114; O-2115; O-2123; O-2072; O-1966A; O-1967B; O-2121; O-2116A; O-2117B; O-2068; O-2090;O-2091	
O-1890	
CP-47497	

See, for example, Gareau et al., 1996; Huffman, 2000; Pertwee et al., 2001; Wiley et al., 2002; Goutopoulos et al., 2002. Many more analogs are known in the art.

In one embodiment, the compound (e.g., the cannabinoid receptor inverse agonist or the cannabinoid receptor neutral antagonist) is selected from compounds of the following formula:



(2)

wherein:

$R^{1'}$ is independently C_{3-20}carbocyclyl, C_{3-20}heterocyclyl, C_{5-20}aryl, and is optionally substituted;

$R^{2'}$ is independently -H, -OH, or an ether group;

$R^{4'}$ is independently C_{1-12}alkyl or substituted C_{1-12}alkyl;

$R^{3'}$, $R^{5'}$, and $R^{6'}$ are independently -H, -OH, halo, C_{1-4}alkyl, or C_{1-4}alkoxy;

and stereoisomers thereof;

and pharmaceutically acceptable salts, solvates, amides, esters, ethers, chemically protected forms, and prodrugs thereof.

In one embodiment, $R^{1'}$ is independently C_{3-20}carbocyclyl; and is optionally substituted.

In one embodiment, $R^{1'}$ is independently C_{6-12}carbocyclyl; and is optionally substituted.

In one embodiment, $R^{1'}$ is independently:

cyclohexyl, cyclohexenyl, cyclohexadienyl, phenyl;

menthanyl, thujanyl;

caranyl, carenyl, caradienyl;

pinanyl, pinenyl, pinadienyl;

bornyl, bornenyl, bornadienyl;

tetralinyl, decalinyl;

or a saturated or unsaturated analogue or derivative thereof;

optionally substituted with one or more of -OH, C_{1-4}alkyl, and C_{1-4}alkoxy.

In one embodiment, $R^{2'}$ is independently -H, -OH, or C_{1-7}alkoxy.

In one embodiment, $R^{2'}$ is independently -H, -OH, -OMe, or -OEt.

In one embodiment, $R^{2'}$ is independently -H or -OH.

In one embodiment, $R^{2'}$ is independently -OH.

In one embodiment, $R^{2'}$ is independently -H.

In one embodiment, $R^{4'}$ is independently C_{4-12}alkyl or substituted C_{4-12}alkyl.

In one embodiment, $R^{4'}$ is independently C_{4-12}alkyl.

In one embodiment, $R^{4'}$ is independently linear or branched C_{4-12}alkyl.

In one embodiment, $R^{4'}$ is independently branched C_{4-12}alkyl.
In one embodiment, $R^{4'}$ is independently $-C(CH_3)_2(CH_2)_nCH_3$, wherein n is 0, 1, 2, 3, 4, 5, 6, or 7.
In one embodiment, $R^{4'}$ is independently $-C(CH_3)_2(CH_2)_nCH_3$, wherein n is 3, 4, 5, 6, or 7.

In one embodiment, each of $R^{3'}$, $R^{5'}$, and $R^{6'}$ is independently -H, -OH, -Me, or -OMe.
In one embodiment, each of $R^{3'}$, $R^{5'}$, and $R^{6'}$ is independently -H or -OH.
In one embodiment, each of $R^{3'}$, $R^{5'}$, and $R^{6'}$ is independently -H.

In one embodiment, $R^{6'}$ is independently as defined for $R^{2'}$; and each of $R^{3'}$ and $R^{5'}$ is independently -H.

For groups which are indicated to be "substituted" or "optionally substituted," certain preferred substituents are described below under the heading "Some Preferred Substituents."

In one embodiment, the compound is as structurally defined above, and additionally has one or more of the functional characteristics defined herein (e.g., has a particular cannabinoid receptor inhibition constant (Ki); is a cannabinoid receptor inverse agonist is a cannabinoid receptor neutral antagonist; is a CB2 inverse agonist; etc.).

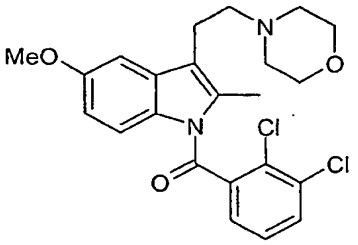
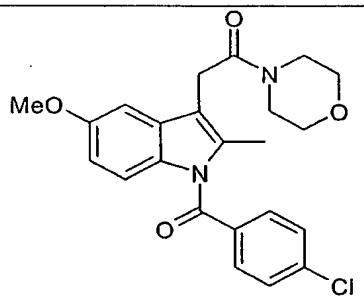
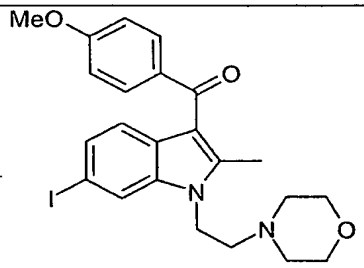
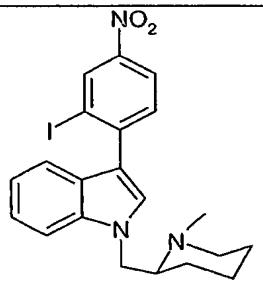
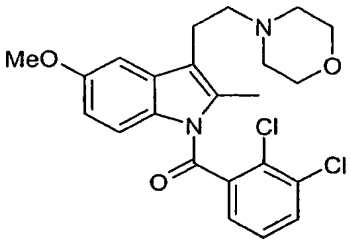
C. Aminoalkylindoles

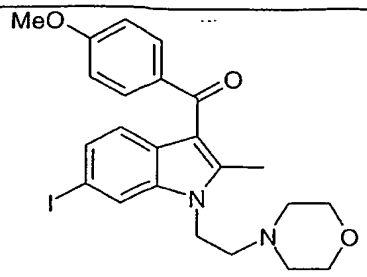
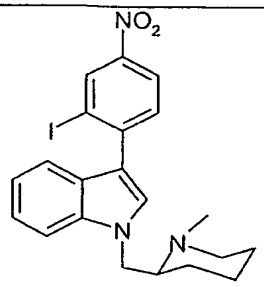
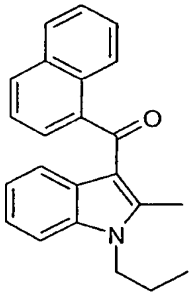
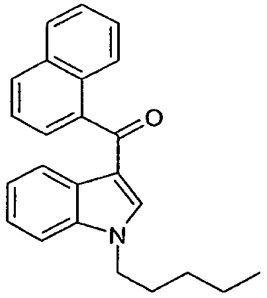
This class of ligands includes those which have an indole core (which may be fused to another ring, e.g., as in WIN55212), often an N-substituted indole core, for example, an N-(amino-alkyl)-substituted indole core.

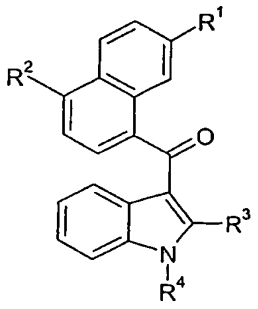
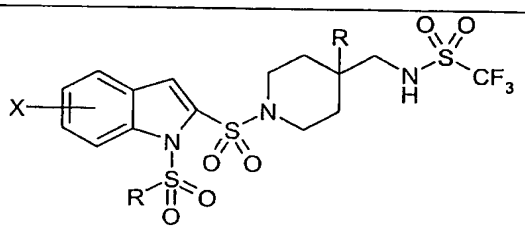
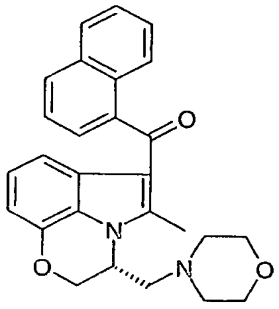
Thus, one aspect of the invention pertains to use of a compound (e.g., a cannabinoid receptor inverse agonist or a cannabinoid receptor neutral antagonist) for the manufacture of a medicament for the treatment of a bone disorder, wherein the compound has an indole core (e.g., is indole or an analogue or derivative thereof).

Another aspect of the present invention pertains to a method of treating a bone disorder comprising administering to a patient in need of treatment thereof a therapeutically effective amount of a compound (e.g., a cannabinoid receptor inverse agonist or a cannabinoid receptor neutral antagonist) having an indole core (e.g., is indole or an analogue or derivative thereof).

Examples of such compounds include, but are not limited to, the following:

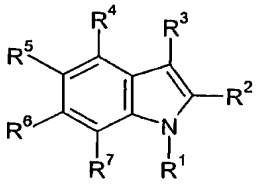
Compound	Structure
L768242	
BML-190	
AM-630	
AM-1241	
L768242	

Compound	Structure
AM-630	
AM-1241	
JWH-015	
JWH-018	

Compound	Structure
JWH-070; JWH-071; JWH-072; JWH-073; JWH-019; JWH-020; JWH-071; JWH-016; JWH-007; JWH-004; JWH-009; JWH-077; JWH-078; JWH-079; JWH-080; JWH-081; JWH-082; JWH-083; JWH-094; JWH-096; JWH-098; JWH-099; JWH-100; JWH-046; JWH-047; JWH-048; JWH-049; JWH-050; JWH-076	
Friary et al., 2003	
WIN-55212-2	

See, for example, Gallant et al., 1996; Melck et al., 2000; Huffman, 2000; Pertwee et al., 2001; Goutopoulos et al., 2002. Many more analogs are known in the art.

In one embodiment, the compound (e.g., the cannabinoid receptor inverse agonist or the cannabinoid receptor neutral antagonist) is selected from compounds of the following formula:



(3)

wherein:

R^1 is independently C_{1-7}alkyl, C_{3-20}heterocyclyl-C_{1-7}alkyl, C_{5-20}aryl-C_{1-7}alkyl, and is optionally substituted;
R^2 is independently -H, -OH, C_{1-4}alkyl, C_{1-4}alkoxy, or halo;
R^3 is independently C_{1-7}alkyl, C_{3-20}heterocyclyl, C_{5-20}aryl, C_{3-20}heterocyclyl-C_{1-7}alkyl, C_{5-20}aryl-C_{1-7}alkyl, C_{1-7}alkyl-acyl, C_{3-20}heterocyclyl-acyl, C_{5-20}aryl-acyl, C_{3-20}heterocyclyl-C_{1-7}alkyl-acyl, or C_{5-20}aryl-C_{1-7}alkyl-acyl; and is optionally substituted;
each of R^4 and R^7 is independently -H, -OH, C_{1-4}alkyl, C_{1-4}alkoxy, or halo;
each of R^5 and R^6 is independently -H, -OH, C_{1-4}alkyl, C_{1-4}alkoxy, or halo;
and stereoisomers thereof;
and pharmaceutically acceptable salts, solvates, amides, esters, ethers, chemically protected forms, and prodrugs thereof.

In one embodiment, R^1 is independently C_{1-7}alkyl, piperidinyl-C_{1-7}alkyl, morpholinyl-C_{1-7}alkyl, phenyl-C_{1-7}alkyl, and is optionally substituted.

In one embodiment, R^2 is independently -H or -Me.
In one embodiment, R^2 is independently -H.

In one embodiment, R^3 is independently piperidinyl-C_{1-7}alkyl, morpholinyl-C_{1-7}alkyl, phenyl; phenyl-acyl; or naphthyl-acyl.

In one embodiment, each of R^4 and R^7 is independently -H, -OH, -Me, -OMe, or halo.
In one embodiment, each of R^4 and R^7 is independently -H.

In one embodiment, each of R^5 and R^6 is independently -H, -OH, -Me, -OMe, or halo.
In one embodiment, each of R^5 and R^6 is independently -H.

For groups which are indicated to be "substituted" or "optionally substituted," certain preferred substituents are described below under the heading "Some Preferred Substituents."

In one embodiment, the compound is as structurally defined above, and additionally has one or more of the functional characteristics defined herein (e.g., has a particular cannabinoid receptor inhibition constant (Ki); is a cannabinoid receptor inverse agonist is a cannabinoid receptor neutral antagonist; is a CB2 inverse agonist; etc.).

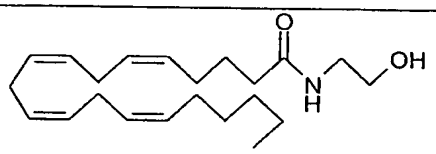
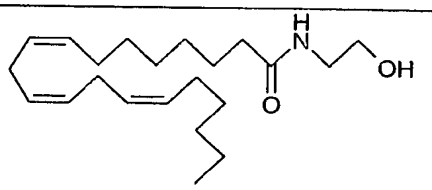
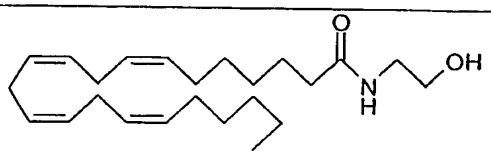
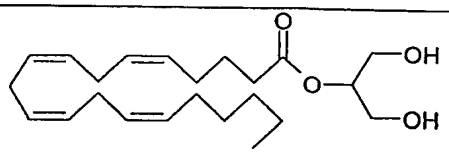
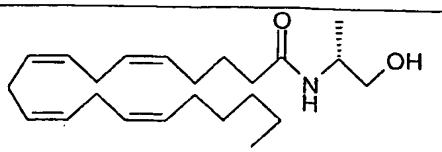
D. Endocannabinoids

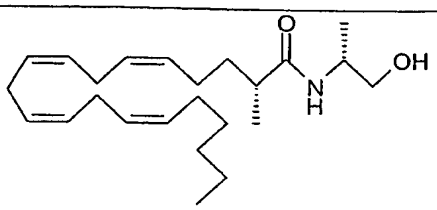
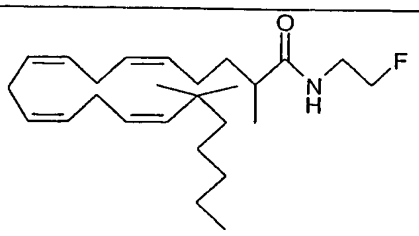
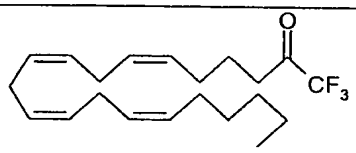
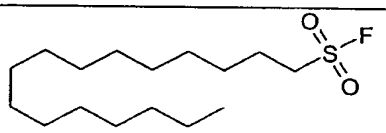
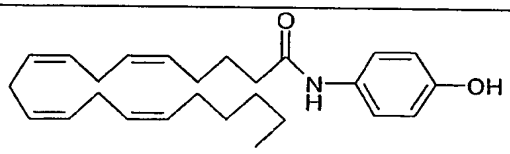
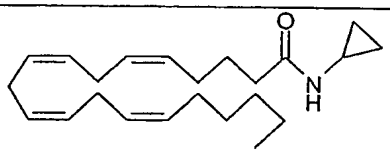
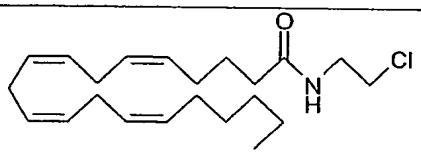
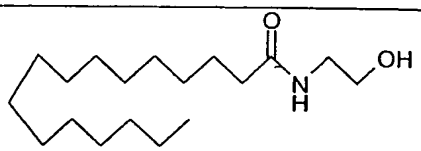
This class of ligands includes those which are structurally similar to the endocannabinoid AEA.

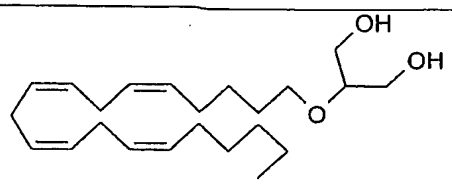
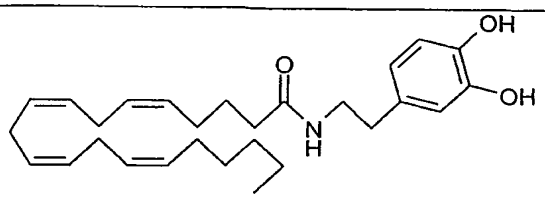
Thus, one aspect of the invention pertains to use of a compound (e.g., a cannabinoid receptor inverse agonist or a cannabinoid receptor neutral antagonist) for the manufacture of a medicament for the treatment of a bone disorder, wherein the compound is AEA or an analogue or derivative thereof.

Another aspect of the present invention pertains to a method of treating a bone disorder comprising administering to a patient in need of treatment thereof a therapeutically effective amount of a compound (e.g., a cannabinoid receptor inverse agonist or a cannabinoid receptor neutral antagonist) that is AEA or an analogue or derivative thereof.

Examples of such compounds include, but are not limited to, the following:

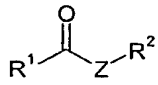
Compound	Structure
arachidonyl ethanolamide (AEA) (anandamide)	
homo-γ-linolenylethanolamide	
7,10,13,16-docosatetranylethyanolamide	
2-arachidonyl-glycerol (2AG)	
R-(+)-methanandamide	

Compound	Structure
AM-1116	
O-1064	
ATFMK	
AM-374	
AM-404	
arachidonylcyclopropylamide (ACPA)	
arahcidonyl-2'-choroethylamide (ACEA)	
Palmitoylethanolamide (PEA)	

Compound	Structure
Noladin ether	
N-[2-(3,4-Dihydroxyphenyl)ethyl]-5Z,8Z,11Z,14Z-eicosatetraeneamide N-arachidonyldopamine (NADA)	

See, for example, Pertwee et al., 2001; Goutopoulos et al., 2002. Many more analogs are known in the art.

In one embodiment, the compound (e.g., the cannabinoid receptor inverse agonist or the cannabinoid receptor neutral antagonist) is selected from compounds of the following formula:

 (4)

wherein:

Z is -NH- or -O-;

R^1 is independently linear or branched, saturated or partially unsaturated C_{12-25}alkyl; and is optionally substituted;

R^2 is independently C_{1-4}alkyl, C_{3-20}heterocyclyl, C_{5-20}aryl, C_{3-20}heterocyclyl-C_{1-4}alkyl, C_{5-20}aryl-C_{1-4}alkyl, hydroxy-C_{1-4}alkyl, hydroxy-C_{3-20}heterocyclyl, hydroxy-C_{5-20}aryl, hydroxy-C_{3-20}heterocyclyl-C_{1-4}alkyl, hydroxy-C_{5-20}aryl-C_{1-4}alkyl, halo-C_{1-4}alkyl, halo-C_{3-20}heterocyclyl, halo-C_{5-20}aryl, halo-C_{3-20}heterocyclyl-C_{1-4}alkyl, halo-C_{5-20}aryl-C_{1-4}alkyl; and is optionally substituted;

and stereoisomers thereof;

and pharmaceutically acceptable salts, solvates, amides, esters, ethers, chemically protected forms, and prodrugs thereof.

In one embodiment, Z is independently -NH-.

In one embodiment, Z is independently -O-.

In one embodiment, R^1 is independently linear or branched, saturated or partially unsaturated C_{18-25}alkyl; and is optionally substituted.

In one embodiment, R^1 is independently linear or branched C_{18-25}alkyl having at least three carbon-carbon double bonds; and is optionally substituted.

In one embodiment, R^1 is independently linear or branched C_{18-25}alkyl having exactly four carbon-carbon double bonds; and is optionally substituted.

In one embodiment, R^1 is independently linear or branched C_{18-25}alkyl having a $-(CH_2-CH=CH)_4-$ group; and is optionally substituted.

In one embodiment, R^1 is independently $-(CH_2)_2-(CH_2-CH=CH)_4-(CH_2)_4-CH_3$.

In one embodiment, R^2 is independently hydroxy-C_{1-4}alkyl, hydroxy-C_{3-20}heterocyclyl, hydroxy-C_{5-20}aryl, hydroxy-C_{3-20}heterocyclyl-C_{1-4}alkyl, hydroxy-C_{5-20}aryl-C_{1-4}alkyl; and is optionally substituted.

In one embodiment, R^2 is independently hydroxy-C_{1-4}alkyl, hydroxy-C_{5-20}aryl, hydroxy-C_{5-20}aryl-C_{1-4}alkyl; and is optionally substituted.

In one embodiment, R^2 is independently $-CH_2CH_2OH$, $-CH(Me)CH_2OH$, -Ph(OH), $-CH_2CH_2(Ph(OH)_2)$.

For groups which are indicated to be "substituted" or "optionally substituted," certain preferred substituents are described below under the heading "Some Preferred Substituents."

In one embodiment, the compound is as structurally defined above, and additionally has one or more of the functional characteristics defined herein (e.g., has a particular cannabinoid receptor inhibition constant (Ki); is a cannabinoid receptor inverse agonist is a cannabinoid receptor neutral antagonist; is a CB2 inverse agonist; etc.).

E. Pyrazoles

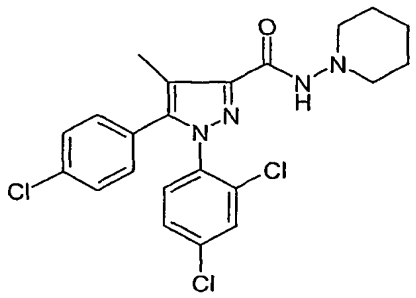
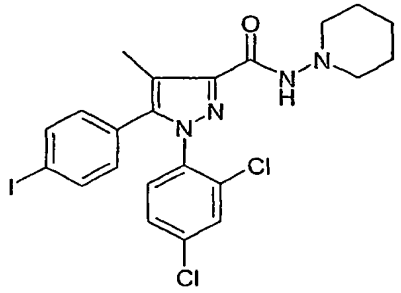
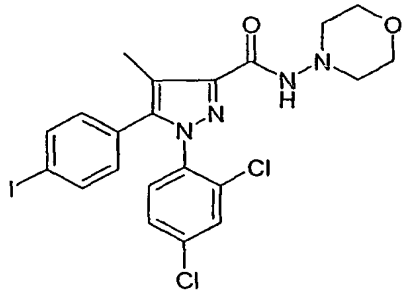
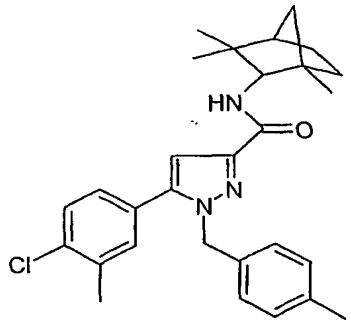
This class of ligands includes those which have a pyrazole core, often a 1,5-disubstituted pyrazole core, for example, a 1,5-diaryl-pyrazole core, for example, a 1,5-diaryl-3-carboxamide pyrazole core.

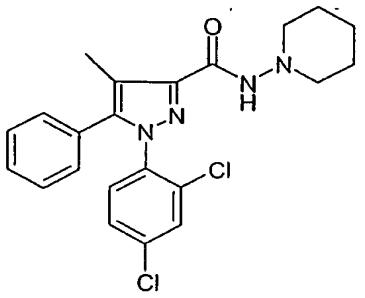
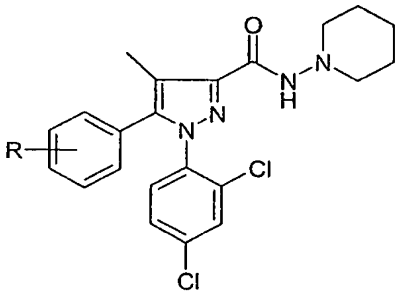
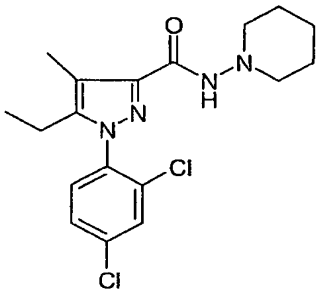
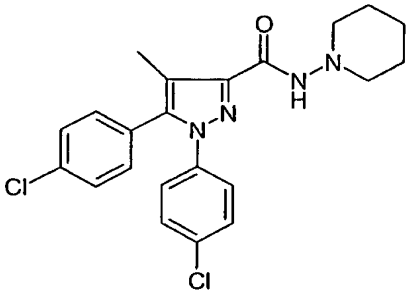
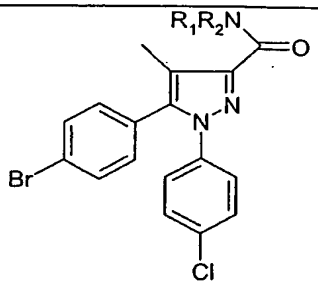
Thus, one aspect of the invention pertains to use of a compound (e.g., a cannabinoid receptor inverse agonist or a cannabinoid receptor neutral antagonist) for the manufacture of a medicament for the treatment of a bone disorder, wherein the compound is pyrazole or an analogue or derivative thereof, e.g., has a pyrazole core, e.g., a 1,5-diaryl-pyrazole core, e.g., a 1,5-diaryl-3-carboxamide pyrazole core.

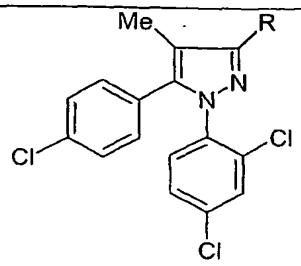
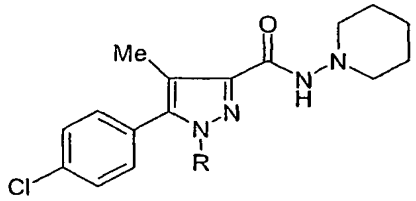
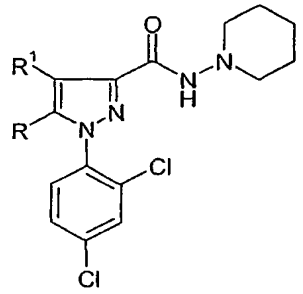
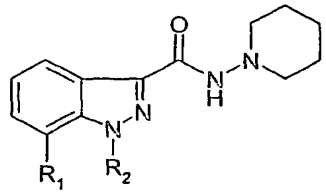
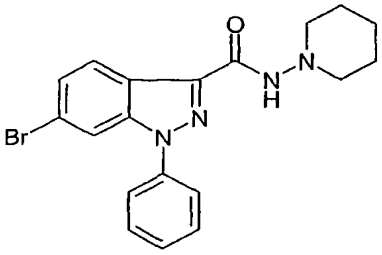
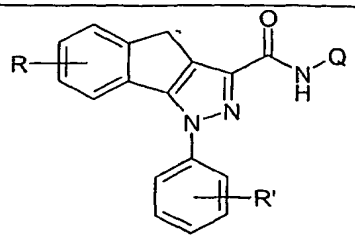
Another aspect of the present invention pertains to a method of treating a bone disorder comprising administering to a patient in need of treatment thereof a therapeutically

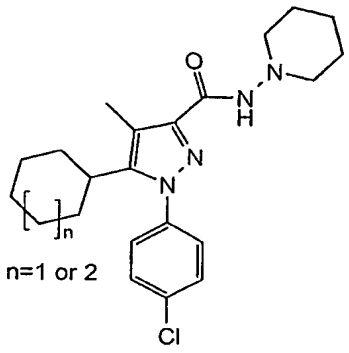
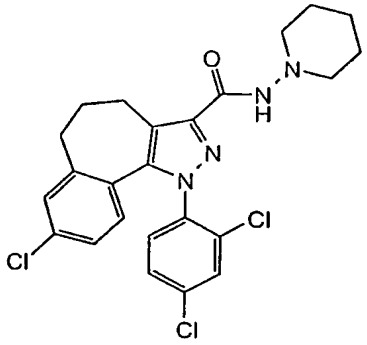
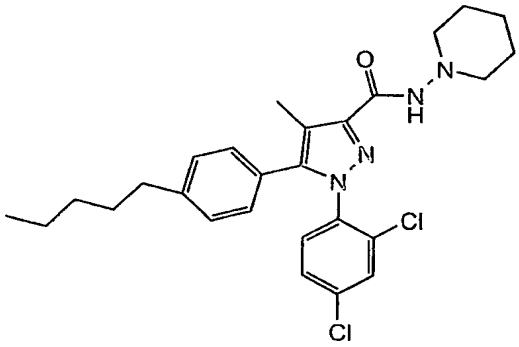
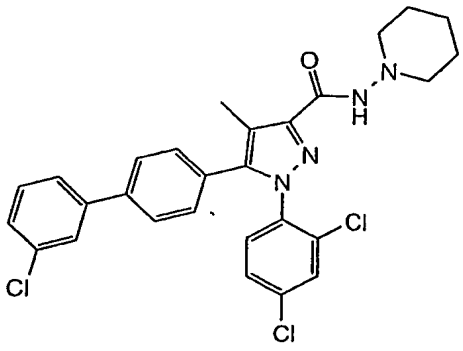
effective amount of a compound (e.g., a cannabinoid receptor inverse agonist or a cannabinoid receptor neutral antagonist) having a-pyrazole core (e.g., is pyrazole or an analogue or derivative thereof).

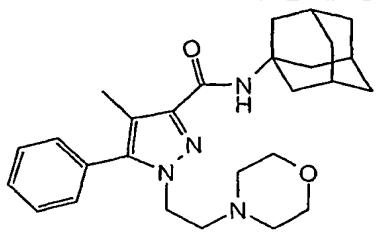
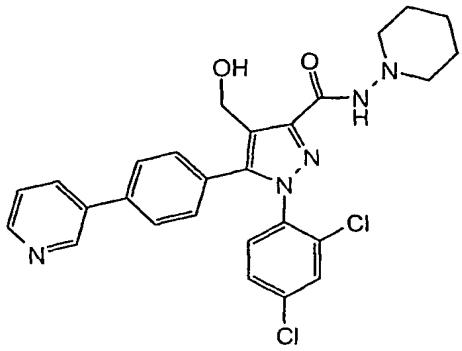
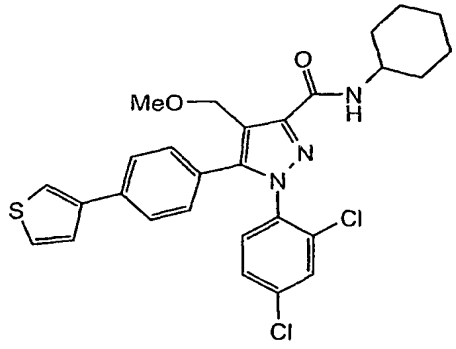
Examples of such compounds include, but are not limited to, the following:

Compound	Structure
SR14176A	
AM-251	
AM-281	
SR144528	

Compound	Structure
Lan-99-07	
Lan-99-08 (para-NO_2); Lan-99-09 (ortho-NO_2); Lan-99-10 (para-NH_2); Lan-99-11 (ortho-NH_2); Lan-99-12 (para-I); Lan-99-13 (ortho-I);	
Lan-99-16	
Lan-99-19	
Lan-99-22; Lan-99-23; Lan-99-24; Lan-99-25; Lan-99-26; Lan-99-27; Lan-99-28; Lan-99-29; Lan-99-30; Lan-99-31	

Compound	Structure
O-848; O-849; O-850; O-852; O-853; O-869; O-870; O-889; O-890; O-909; O-910; O-1043;O-1269; O-1270; O-1271; O-1272; O-1398; O-1399; O-1876; O-1877	
O-1253; O-1254; O-1255; O-1300	
O-1302; O-1559; O-1690; O-1691; O-1704; O-1710	
O-1247; O-1248; O-1654; O-1655; O-1412; O-1343	
(Makriyannis et al., 2003b)	
Mussinu 1A-1R (Mussinu et al., 2003)	

Compound	Structure
(Krishnamurthy et al., 2004)	
NESS 0327 (Ruiu et al., 2003)	
O-1302 (Martin et al., 2003a)	
(Makriyannis, A., et al., 2003a)	

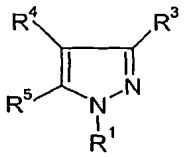
Compound	Structure
(Makriyannis, A., et al., 2003a)	
(Makriyannis, A., et al., 2003a)	
(Makriyannis, A., et al., 2003a)	

See, for example: Gatley et al., 1996; Lan et al., 1999; Pertwee et al., 2001; Wiley et al., 2001; Goutopoulos et al., 2002; Shim et al., 2002; Bass et al., 2002; Mussinu et al., 2003; Krishnamurthy et al., 2004; Ruiu et al., 2003; Martin et al., 2003a; Makriyannis, A., et al., 2003a. Many more analogs are known in the art.

In one embodiment, the compound is a pyrazole compound and is: celecoxib, deracoxib, or tepoxalin; or an analog or derivative thereof; or a pharmaceutically acceptable salt, solvate, amide, ester, ether, chemically protected form, or prodrug thereof.

Some Preferred Pyrazoles

In one embodiment, the compound (e.g., the cannabinoid receptor inverse agonist or the cannabinoid receptor neutral antagonist) is selected from compounds of the following formula:



(5)

wherein:

R^1 is independently:

C_{3-20}carbocyclyl,

C_{3-20}heterocyclyl,

C_{5-20}aryl, or

C_{5-20}aryl-C_{1-4}alkyl;

and is optionally substituted;

R^4 is independently:

-H,

C_{1-4}alkyl,

C_{3-20}heterocyclyl,

C_{5-20}aryl, or

C_{5-20}aryl-C_{1-4}alkyl;

and is optionally substituted;

R^5 is independently:

C_{1-4}alkyl,

C_{3-20}carbocyclyl,

C_{3-20}heterocyclyl,

C_{5-20}aryl, or

C_{5-20}aryl-C_{1-4}alkyl;

and is optionally substituted;

R^3 is independently:

amino-acyl;

amino-amino-acyl;

acyl;

acyl-oxy;

ether; or

and is optionally substituted;

and stereoisomers thereof;

and pharmaceutically acceptable salts, solvates, amides, esters, ethers, chemically protected forms, and prodrugs thereof.

Note the non-symmetry of the pyrazole ring, and the non-equivalence of the R^3 and R^4 substituents.

The Substituent R^1

In one embodiment, R^1 is independently C_{5-20}aryl or C_{5-20}aryl-C_{1-4}alkyl; and is optionally substituted.

In one embodiment, R^1 is independently phenyl or benzyl; and is optionally substituted.

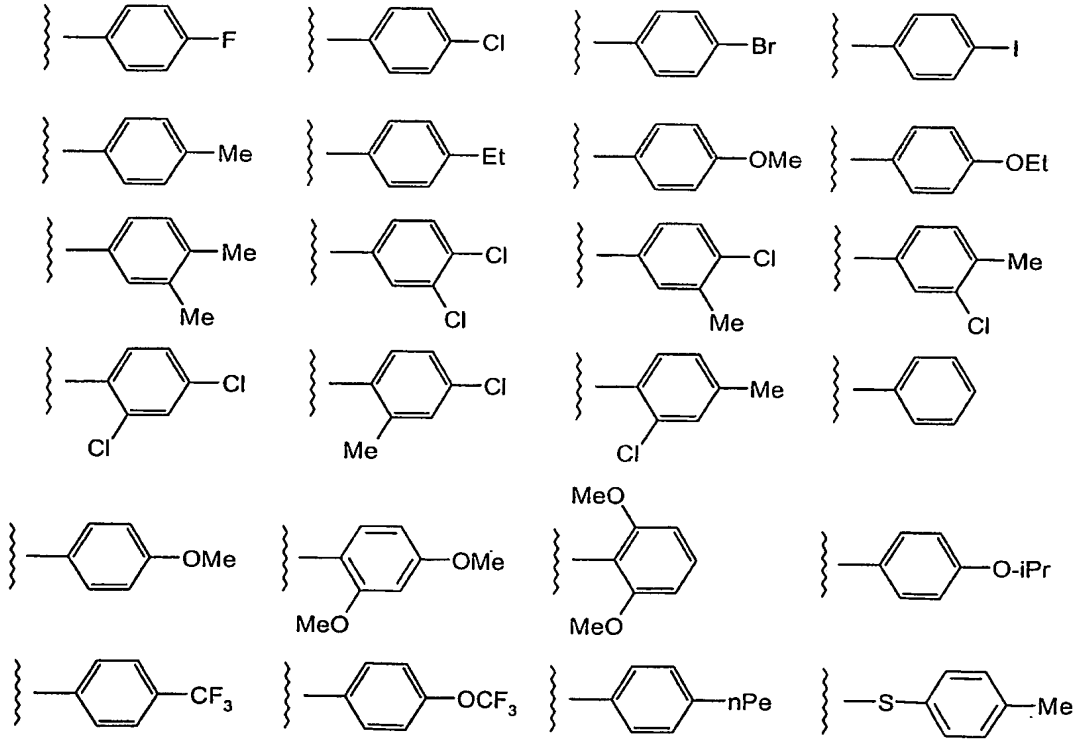
In one embodiment, R^1 is independently C_{5-20}aryl; and is optionally substituted.

In one embodiment, R^1 is independently C_{5-7}aryl; and is optionally substituted.

In one embodiment, R^1 is independently C_6aryl; and is optionally substituted.

In one embodiment, R^1 is independently phenyl; and is optionally substituted.

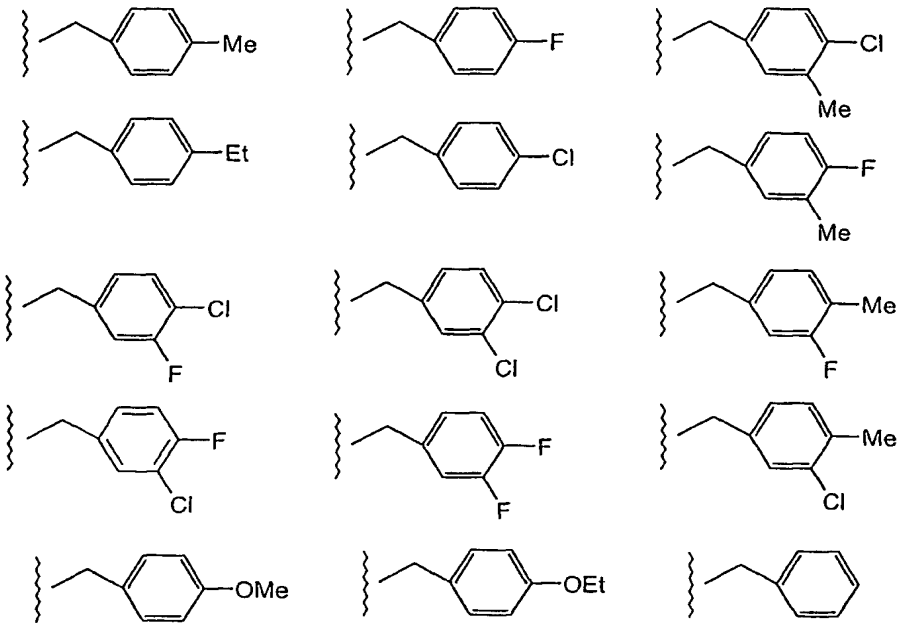
In one embodiment, R^1 is independently selected from ("examples of optionally substituted phenyl groups"):



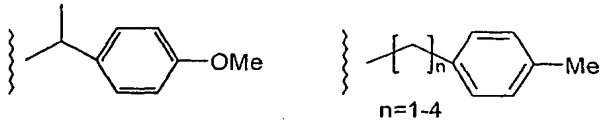
In one embodiment, R^1 is independently C_{5-20}aryl-C_{1-4}alkyl; and is optionally substituted.

In one embodiment, R^1 is independently C_{5-7}aryl-C_{1-4}alkyl; and is optionally substituted.
In one embodiment, R^1 is independently C_6aryl-C_{1-4}alkyl; and is optionally substituted.
In one embodiment, R^1 is independently benzyl; and is optionally substituted.

In one embodiment, R^1 is independently selected from ("examples of optionally substituted benzyl groups"):



In one embodiment, R^1 is independently selected from:



The Substituent R^5

In one embodiment, R^5 is independently:
C_{3-20}carbocyclyl,
C_{3-20}heterocyclyl,
C_{5-20}aryl, or
C_{5-20}aryl-C_{1-4}alkyl;
and is optionally substituted.

In one embodiment, R^5 is independently C_{5-20}aryl or C_{5-20}aryl-C_{1-4}alkyl; and is optionally substituted.

In one embodiment, R^5 is independently phenyl or benzyl; and is optionally substituted.

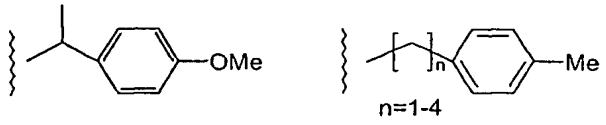
In one embodiment, R^5 is independently C_{5-20}aryl; and is optionally substituted.
In one embodiment, R^5 is independently C_{5-7}aryl; and is optionally substituted.
In one embodiment, R^5 is independently C_6aryl; and is optionally substituted.
In one embodiment, R^5 is independently phenyl; and is optionally substituted.

In one embodiment, R^5 is independently selected from the "examples of optionally substituted phenyl groups" listed above for R^1.

In one embodiment, R^5 is independently C_{5-20}aryl-C_{1-4}alkyl; and is optionally substituted.
In one embodiment, R^5 is independently C_{5-7}aryl-C_{1-4}alkyl; and is optionally substituted.
In one embodiment, R^5 is independently C_6aryl-C_{1-4}alkyl; and is optionally substituted.
In one embodiment, R^5 is independently benzyl; and is optionally substituted.

In one embodiment, R^5 is independently selected from the "examples of optionally substituted benzyl groups" listed above for R^1.

In one embodiment, R^5 is independently selected from:



In one embodiment, R^5 is independently C_{1-4}alkyl; and is optionally substituted.
In one embodiment, R^5 is independently -Me, -Et, -nPr, -iPr, -nBu, -sBu, -iBu, -tBu, or -nPe.

All combinations of R^1 (as defined herein) and R^5 (as defined herein) are explicitly disclosed herein. Some preferred combinations of R^1 and R^5 are mentioned next.

In one embodiment, R^1 is independently C_{5-20}aryl-C_{1-4}alkyl, and is optionally substituted and R^5 is independently C_{5-20}aryl, and is optionally substituted.

In one embodiment, R^1 is independently benzyl, and is optionally substituted and R^5 is independently phenyl, and is optionally substituted.

In one embodiment, R^1 is independently C_{5-20}aryl, and is optionally substituted, and R^5 is independently C_{5-20}aryl-C_{1-4}alkyl, and is optionally substituted.

In one embodiment, R^1 is independently phenyl, and is optionally substituted, and R^5 is independently benzyl, and is optionally substituted.

In one embodiment, R^1 is independently C_{5-20}aryl, and is optionally substituted and R^5 is independently C_{5-20}aryl, and is optionally substituted.

In one embodiment, R^1 is independently phenyl, and is optionally substituted and R^5 is independently phenyl, and is optionally substituted.

In one especially preferred embodiment, R^1 and R^5 are as defined in the "combinations" immediately above, and R^3 is independently: amino-acyl; or amino-amino-acyl; and is optionally substituted.

The Substituent R^4

In one embodiment, R^4 is independently C_{1-4}alkyl; and is optionally substituted (e.g., $-CH_2$-OMe, $-CH_2$-F, $-CH_2$-NHMe, etc.; see below).

In one embodiment, R^4 is independently C_{3-20}heterocyclyl; and is optionally substituted.

In one embodiment, R^4 is independently C_{5-7}aryl; and is optionally substituted.
In one embodiment, R^4 is independently C_6aryl; and is optionally substituted.
In one embodiment, R^4 is independently phenyl; and is optionally substituted.

In one embodiment, R^4 is independently C_{5-7}aryl-C_{1-4}alkyl; and is optionally substituted.
In one embodiment, R^4 is independently C_6aryl-C_{1-4}alkyl; and is optionally substituted.
In one embodiment, R^4 is independently benzyl; and is optionally substituted.

In one embodiment, R^4 is independently -H or C_{1-4}alkyl; and is optionally substituted.

In one embodiment, R^4 is independently -H, -Me, -Et, -Ph, or $-CH_2Ph$.
In one embodiment, R^4 is independently -H, -Me, or -Et.
In one embodiment, R^4 is independently -H or -Me.
In one embodiment, R^4 is independently -Me.
In one embodiment, R^4 is independently -H.

In one embodiment, R^4 and R^5 together form a ring having from 5 to 7 ring atoms and fused to the parent pyrazole group; which ring is optionally substituted.

In one embodiment, R^4 and R^5 together form a phenyl ring fused to the parent pyrazole group; which phenyl ring is optionally substituted.

The Substituent R^3 - Amino-Acyl

In one embodiment, R^3 is independently amino-acyl; and is optionally substituted.

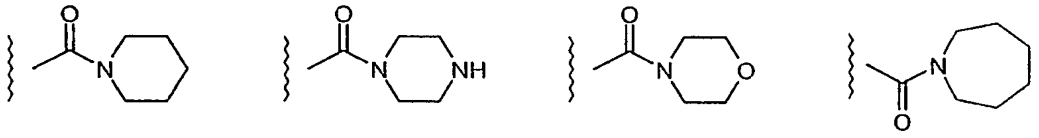
In one embodiment, R^3 is independently:

C_{3-8}cycloamino-acyl,
C_{3-20}carbocyclyl-amino-acyl,
C_{3-20}heterocyclyl-amino-acyl,
C_{1-7}alkyl-amino-acyl,
C_{5-20}aryl-amino-acyl,
C_{5-20}aryl-C_{1-7}alkyl-amino-acyl,
C_{5-20}heteroarylamino-acyl,
and is optionally substituted.

In one embodiment, R^3 is independently C_{3-8}cycloamino-acyl; and is optionally substituted.

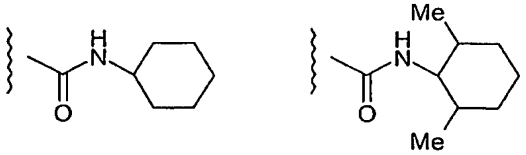
In one embodiment, R^3 is independently piperidino-acyl, piperazino-acyl, morpholino-acyl, azepino-acyl; and is optionally substituted.

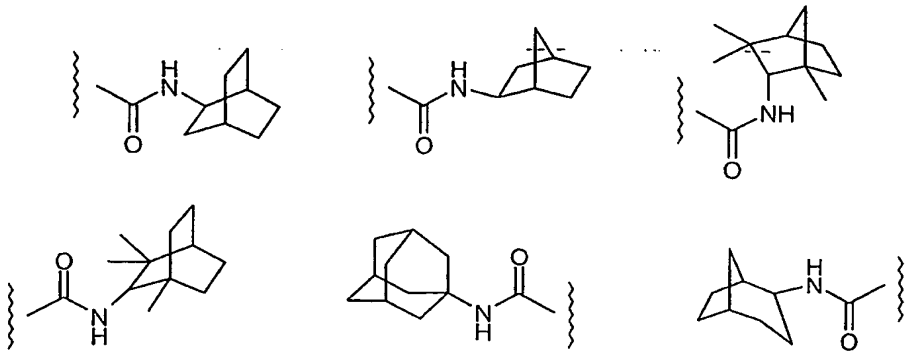
In one embodiment, R^3 is independently selected from:



In one embodiment, R^3 is independently C_{3-20}carbocyclyl-amino-acyl; and is optionally substituted.

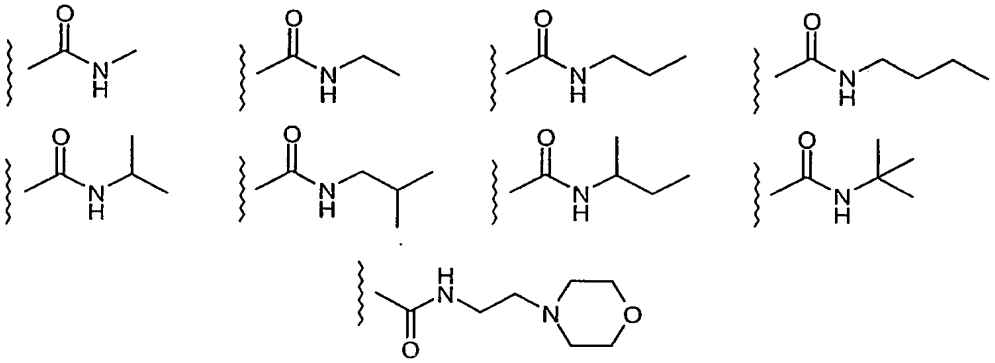
In one embodiment, R^3 is independently selected from:





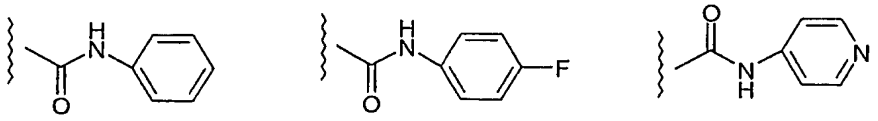
In one embodiment, R^3 is independently C_{1-7}alkyl-amino-acyl; and is optionally substituted.

In one embodiment, R^3 is independently selected from:



In one embodiment, R^3 is independently C_{5-20}aryl-amino-acyl; and is optionally substituted.

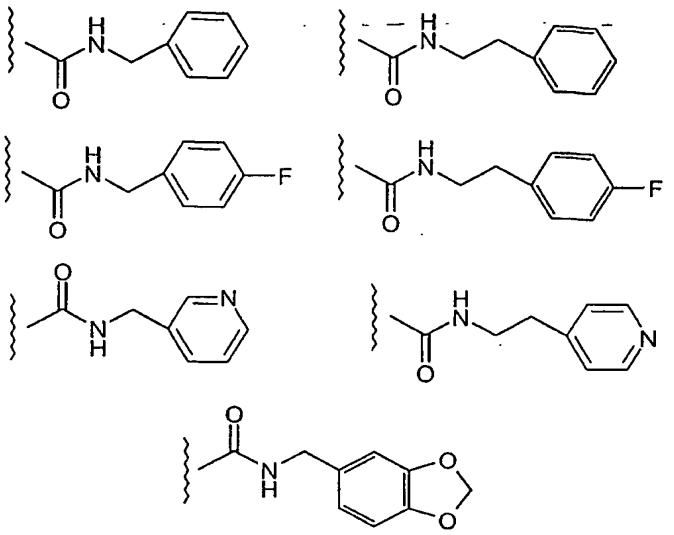
In one embodiment, R^3 is independently selected from:



In one embodiment, R^3 is independently phenyl-amino-acyl; and is optionally substituted.

In one embodiment, R^3 is independently C_{5-20}aryl-C_{1-7}alkyl-amino-acyl; and is optionally substituted.

In one embodiment, R^3 is independently selected from:

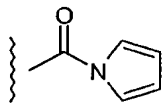


In one embodiment, R^3 is independently benzyl-amino-acyl; and is optionally substituted.

In one embodiment, R^3 is independently C_{5-20}heteroarylamino-acyl; and is optionally substituted. (A C_{5-20}heteroarylamino group is a C_{5-20}heteroaryl group having at least one aromatic nitrogen ring atom, and linked via that atom, e.g., as in pyrrolo.)

In one embodiment, R^3 is independently pyrrolo-amino-acyl; and is optionally substituted.

In one embodiment, R^3 is independently selected from:



<u>The Substituent R^3 - Amino-Amino-Acyl</u>

In one embodiment, R^3 is independently amino-amino-acyl; and is optionally substituted.

In one embodiment, R^3 is independently:

C_{3-8}cycloamino-amino-acyl,
C_{3-20}carbocyclyl-amino-amino-acyl,
C_{3-20}heterocyclyl-amino-amino-acyl,
C_{1-7}alkyl-amino-amino-acyl,
C_{5-20}aryl-amino-amino-acyl,
C_{5-20}aryl-C_{1-7}alkyl-amino-amino-acyl,

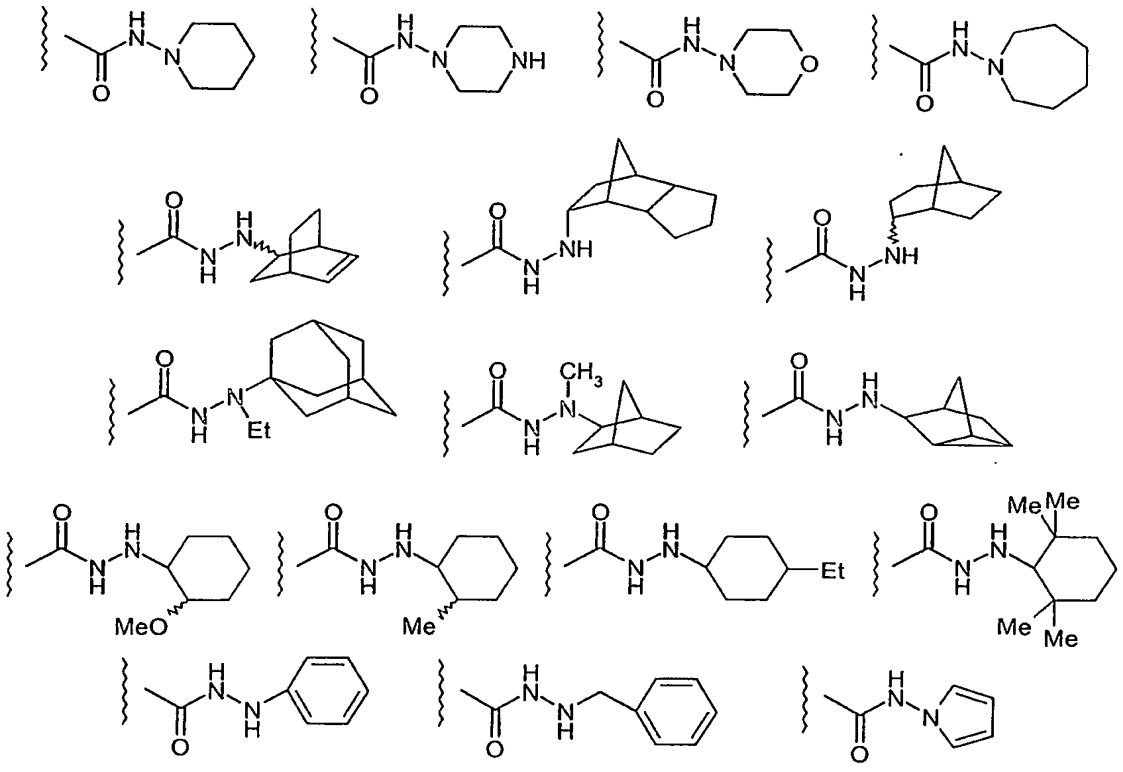
C_{5-20}heterarylamino-amino-acyl,
and is optionally substituted.

In one embodiment, R^3 is independently C_{3-8}cycloamino-amino-acyl; and is optionally substituted.

In one embodiment, R^3 is independently piperidino-amino-acyl, piperazino-amino-acyl, morpholino-amino-acyl, or azepino-amino-acyl; and is optionally substituted.

In one embodiment, R^3 is independently phenyl-amino-amino-acyl, benzyl-amino-amino-acyl, or pyrrolo-amino-acyl; and is optionally substituted.

In one embodiment, R^3 is independently selected from:



The Substituent R^3 - Acyl

In one embodiment, R^3 is independently acyl; and is optionally substituted.

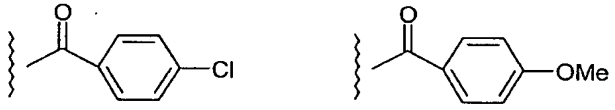
In one embodiment, R^3 is independently:
C_{1-7}alkyl-acyl,

C_{5-20}aryl-acyl, or
C_{5-20}aryl-C_{1-7}alkyl-acyl;-
and is optionally substituted.

In one embodiment, R^3 is independently:
C_{5-20}aryl-acyl, or
C_{5-20}aryl-C_{1-7}alkyl-acyl,
and is optionally substituted.

In one embodiment, R^3 is independently C_{5-20}aryl-acyl, and is optionally substituted.
In one embodiment, R^3 is independently phenyl-acyl, and is optionally substituted.
In one embodiment, R^3 is independently benzyl-acyl, and is optionally substituted.

In one embodiment, R^3 is independently selected from:



The Substituent R^3 - Acyl-Oxy

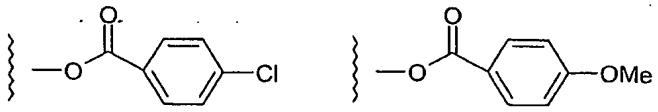
In one embodiment, R^3 is independently acyl-oxy; and is optionally substituted.

In one embodiment, R^3 is independently:
C_{1-7}alkyl-acyl-oxy,
C_{5-20}aryl-acyl-oxy, or
C_{5-20}aryl-C_{1-7}alkyl-acyl-oxy;
and is optionally substituted.

In one embodiment, R^3 is independently:
C_{5-20}aryl-acyl-oxy, or
C_{5-20}aryl-C_{1-7}alkyl-acyl-oxy,
and is optionally substituted.

In one embodiment, R^3 is independently C_{5-20}aryl-acyl-oxy, and is optionally substituted.
In one embodiment, R^3 is independently phenyl-acyl-oxy, and is optionally substituted.
In one embodiment, R^3 is independently benzyl-acyl-oxy, and is optionally substituted.

In one embodiment, R^3 is independently selected from:



The Substituent R^3 - Ether

In one embodiment, R^3 is independently ether; and is optionally substituted.

In one embodiment, R^3 is independently:
C_{1-7}alkyl-oxy (C_{1-7}alkoxy),
C_{5-20}aryl-oxy, or
C_{5-20}aryl-C_{1-7}alkyl-oxy;
and is optionally substituted.

In one embodiment, R^3 is independently C_{1-7}alkoxy; and is optionally substituted.

In one embodiment, R^3 is independently selected from:
-O-Me, -O-Et, -O-nPr, -O-iPr, -O-nBu, -O-sBu, -O-iBu, -O-tBu, and -O-nPe.

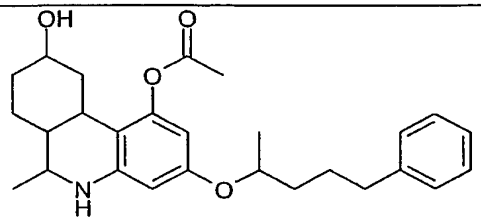
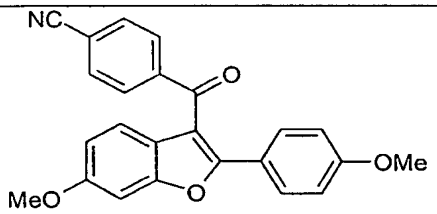
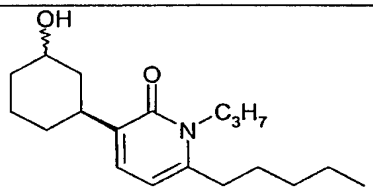
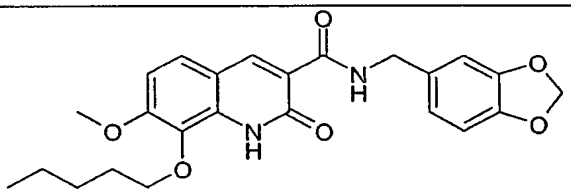
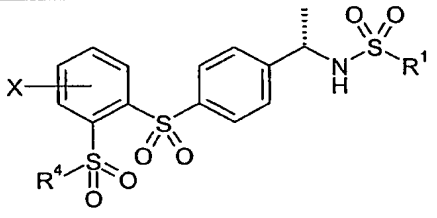
For groups which are indicated to be "substituted" or "optionally substituted," certain preferred substituents are described below under the heading "Some Preferred Substituents."

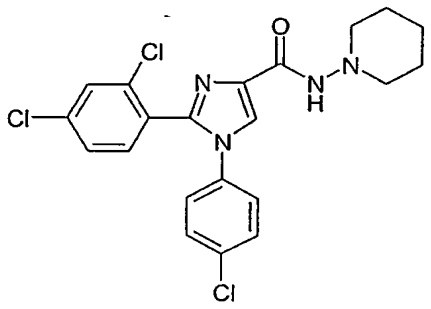
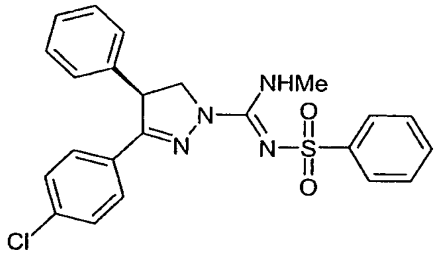
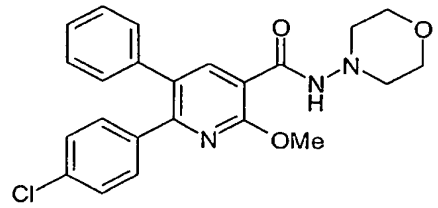
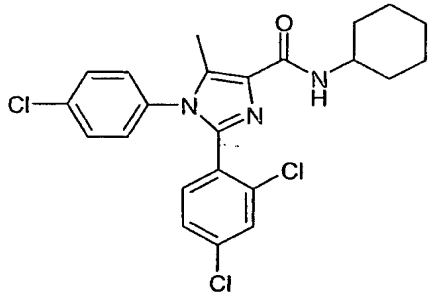
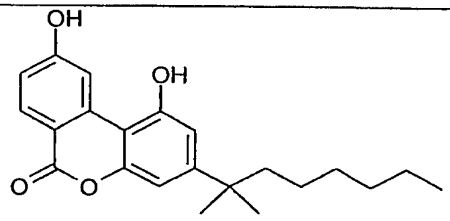
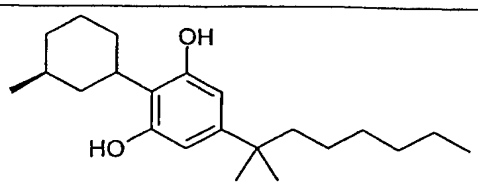
In one embodiment, the compound is as structurally defined above, and additionally has one or more of the functional characteristics defined herein (e.g., has a particular cannabinoid receptor inhibition constant (Ki); is a cannabinoid receptor inverse agonist is a cannabinoid receptor neutral antagonist; is a CB2 inverse agonist; etc.).

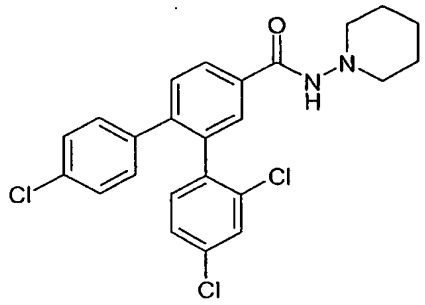
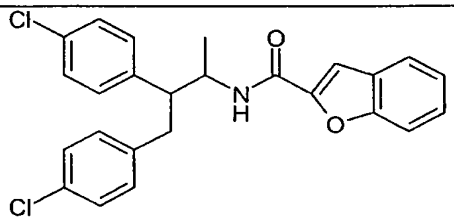
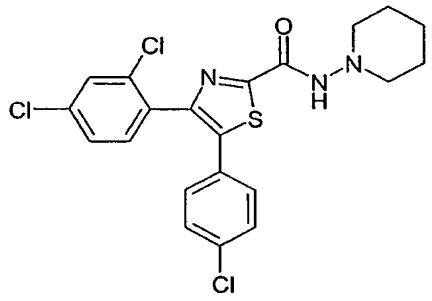
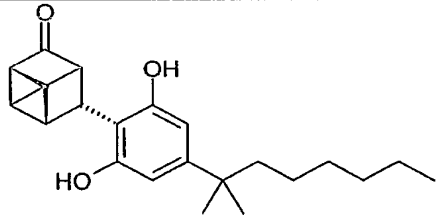
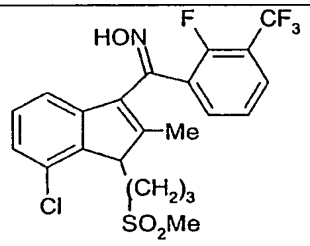
Many pyrazole compounds have been described as possible treatments for osteoporosis and other bone diseases. See, for example: Anantanarayan et al., 1999; Anantanarayan et al., 2002; Anantanarayan et al., 2003a; Anantanarayan et al., 2003b; Blake et al., 1997; Didierlaurent et al., 1999; Dragovich et al., 2003; Green et al., 2003; Hale et al., 2003; Hanson et al., 2002; Hanson et al., 2003; Hanson et al., 2000; Huebner et al., 2001; Kapadia et al., 2002; Kolasa et al., 2002; Weier et al., 1999; Weier et al., 2003. However, the presently claimed pyrazole compounds are structurally distinct from the pyrazole compounds previously associated with osteoporosis, and furthermore, the pyrazole compounds known for treatment of bone diseases are not known to be CB receptor inverse agonists or neutral antagonists.

F. Miscellaneous Compounds

This class of ligands includes those which do not fall within the previous classes. Examples of such compounds include, but are not limited to, the following:

Compound	Structure
CP-50556 (L-nantradol)	
LY320135 (see, e.g., Felder et al., 1998)	
Pyridone-5 & Pyridone-21 (see, e.g., Huffman et al., 2001)	
JTE-907 (see, e.g., Iwamura et al., 2001; Inaba et al., 2001)	
Kozlowski et al., 2003	

Compound	Structure
Kruse et al., 2003b	
Kruse et al., 2003a	
Finke et al., 2003	
Hagmann et al., 2003a	
Khanolkar et al., 2001	
Martin et al., 2003b (O-1797)	

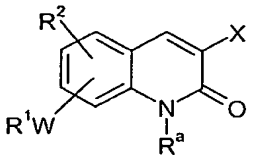
Compound	Structure
Barth et al., 2003a	
Hagmann et al., 2003b	
Lange et al., 2003	
Garzon et al., 2003	
Barth et al., 2003b	

Thus, one aspect of the invention pertains to use of a compound for the manufacture of a medicament for the treatment of a bone disorder, wherein the compound has a 2-oxoquinoline core (e.g., is 2-oxoquinoline or an analogue or derivative thereof).

5

Another aspect of the present invention pertains to a method of treating a bone disorder comprising administering to a patient in need of treatment thereof a therapeutically effective amount of compound (e.g., a cannabinoid receptor inverse agonist or a cannabinoid receptor neutral antagonist) having a 2-oxoquinoline core (e.g., is 2-oxoquinoline or an analogue or derivative thereof).

In one embodiment (see, e.g., Inaba et al., 2001; Iwamura et al., 2001), the compound (e.g., the cannabinoid receptor inverse agonist or the cannabinoid receptor neutral antagonist) is selected from compounds (2-oxoquinolines) of the following formula:



(6)

wherein:

W is -O-, -S(O)$_t$-, -CR^{3}R^4-, -NR^5-, -NR^{5}CO-, -CONR^5-, -COO-, or -OCO-
(where R^3 and R^4 may be identical or different and are hydrogen atom or C_{1-7}alkyl;
R^5 is hydrogen atom or C_{1-7}alkyl; and t is 0, 1 or 2);

R^1 represents hydrogen atom, C_{1-7}alkyl, C_{1-7}alkenyl, C_{1-7}alkynyl, C_{5-20}aryl, C_{5-20}aryl-C_{1-7}alkyl, C_{5-20}heteroaryl, C_{5-20}heteroaryl-C_{1-7}alkyl, C_{1-7}cycloalkyl, or C_{1-7}cycloalkyl-C_{1-7}alkyl;
each group of R^1, except hydrogen atom, may be substituted or unsubstituted with C_{1-7}alkyl-amino, amino, hydroxy, C_{1-7}alkoxy, carboxy, C_{1-7}alkoxycarbonyl, acyl, acyloxy, acylthio, mercapto, C_{1-7}alkyl-thio, C_{1-7}alkyl-sulfinyl or C_{1-7}alkyl-sulfonyl;
each group, except hydrogen atom and C_{1-7}alkyl, may be substituted or unsubstituted with C_{1-7}alkyl;

R^2 represents hydrogen atom, C_{1-7}alkyl, -OR^6
(where R^6 represents hydrogen atom, C_{1-7}alkyl, C_{1-7}alkenyl, C_{1-7}alkynyl, C_{5-20}aryl, C_{5-20}aryl-C_{1-7}alkyl, C_{5-20}heteroaryl, C_{5-20}heteroaryl-C_{1-7}alkyl, C_{1-7}cycloalkyl or C_{1-7}cycloalkyl-C_{1-7}alkyl),
-NR^{7}R^8
(where R^7 and R^8 may be identical or different and are hydrogen atom, C_{1-7}alkyl, C_{1-7}alkenyl, C_{1-7}alkynyl, acyl, C_{5-20}aryl, C_{5-20}aryl-C_{1-7}alkyl, C_{5-20}heteroaryl, C_{5-20}heteroaryl-C_{1-7}alkyl, C_{1-7}cycloalkyl or C_{1-7}cycloalkyl-C_{1-7}alkyl; or R^7 and R^8, together with the adjacent nitrogen atom, can form a C_{5-20}heteroaryl); or
-(CH$_2$)$_{u'}$-S(O)$_u$R^9
(where R^9 represents hydrogen atom, C_{1-7}alkyl, C_{1-7}alkenyl or C_{1-7}alkynyl,
each of u and u' independently is 0, 1 or 2);

each group of R^2, except hydrogen atom, may be substituted or unsubstituted with C_{1-7}alkyl-amino, amino, hydroxy, C_{1-7}alkoxy, C_{1-7}alkoxycarbonyl, acyl, acyloxy, acylthio, mercapto, C_{1-7}alkylthio, C_{1-7}alkyl-sulfinyl or C_{1-7}alkyl-sulfonyl;

each group, except hydrogen atom and C_{1-7}alkyl, may be substituted or unsubstituted with C_{1-7}alkyl;

R^a represents hydrogen atom or C_{1-7}alkyl;

X represents -$COOR^b$, -$CONH_2$, -$CONR^c$-$(Alk^a)_r$-R, -$(CH_2)_p$-OC(=Y)-NR^d-$(Alk^b)_s$-R, -$(CH_2)_q$-NR^e-C(=Z)-$(NR^f)_w(Alk^c)_v$-R, -$(CH_2)_p$-OH or -(CH_2)-$NR^eR^{e'}$

(where each of R^b, R^c, R^d, and R^f independently represents hydrogen atom or C_{1-7}alkyl;

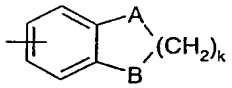
each of R^e and $R^{e'}$ independently represents hydrogen atom or C_{1-7}alkyl;

or R^e and $R^{e'}$, together with the adjacent nitrogen atom, can form a C_{5-20}heteroaryl;

each of Alk^a, Alk^b and Alk^c independently represents C_{1-7}alkylene or C_{1-7}alkenylene;

each of the C_{1-7}alkylene and C_{1-7}alkenylene may be substituted or unsubstituted with hydroxy, carboxy, C_{1-7}alkoxycarbonyl, C_{1-7}alkyl (the C_{1-7}alkyl may be substituted or unsubstituted with hydroxy, C_{1-7}alkoxy or C_{1-7}alkyl-thio) or -$CONR^{10}R^{11}$ (where R^{10} and R^{11} may be identical or different and are hydrogen atom or C_{1-7}alkyl; or R^{10} and R^{11}, together with the adjacent nitrogen atom, can form a C_{5-20}heteroaryl);

R represents C_{5-20}aryl, C_{5-20}heteroaryl, C_{1-7}cycloalkyl, benzene-condensed C_{1-7}cycloalkyl or



where A and B independently represent oxygen atom, nitrogen atom or sulfur atom;

k is an integer of 1-3;

each of the C_{5-20}aryl and C_{5-20}heteroaryl may be substituted or unsubstituted with a C_{1-7}alkyl substituted or unsubstituted with hydroxy or may be substituted or unsubstituted with a hydroxy, C_{1-7}alkoxy, C_{1-7}alkenyloxy, acyl, acyloxy, halogen atom, nitro, amino, sulfonamide, C_{1-7}alkylamino, C_{5-20}aryl-C_{1-7}alkyloxy, pyridyl, piperidino, carboxy, C_{1-7}alkoxycarbonyl, acylamino, aminocarbonyl, cyano or glucuronic acid residue;

the C_{1-7}cycloalkyl may be substituted or unsubstituted with a hydroxy, C_{1-7}alkoxy or =O;

the benzene-condensed C_{1-7}cycloalkyl may be substituted or unsubstituted with a hydroxy or C_{1-7}alkoxy;

each of r, s, v and w independently is 0 or 1;

each of Y and Z independently represents a nitrogen atom, oxygen atom or sulfur atom; and

each of p and q independently represents an integer of 1-4;

and stereoisomers thereof;

and pharmaceutically acceptable salts, solvates, amides, esters, ethers, chemically protected forms, and prodrugs thereof.

For groups which are indicated to be "substituted" or "optionally substituted," certain preferred substituents are described below under the heading "Some Preferred Substituents."

In one embodiment, the compound is as structurally defined above, and additionally has one or more of the functional characteristics defined herein (e.g., has a particular cannabinoid receptor inhibition constant (Ki); is a cannabinoid receptor inverse agonist; is a cannabinoid receptor neutral antagonist; is a CB2 inverse agonist; etc.).

Some Preferred Substituents

In many of the embodiments discussed above, chemical moieties are referred to as "substituted" or "optionally substituted," that is, (optionally) bearing one or more substituents. In one embodiment, each of those substituents, if present, is independently selected from:

(1) carboxylic acid; (2) ester; (3) amido; (4) acyl; (5) halo; (6) cyano; (7) nitro; (8) hydroxy; (9) ether; (10) thiol; (11) thioether; (12) acyloxy; (13) amino; (14) acylamino; (15) aminoacylamino; (16) sulfonamino; (17) sulfonyl; (18) sulfonate; (19) sulfonamido; (20) C_{5-20}aryl-C_{1-7}alkyl; (21) C_{5-20}aryl; (22) C_{3-20}heterocyclyl; (23) C_{1-7}alkyl; (24) oxo; (25) imino; (26) hydroxyimino.

In one embodiment, each of those substituents is independently selected from:

(1) -C(=O)OH;
(2) -C(=O)OR^1, wherein R^1 is independently as defined in (20), (21), (22) or (23);
(3) -C(=O)NR^2R^3, wherein each of R^2 and R^3 is independently -H; or as defined in (20), (21), (22) or (23); or R^2 and R^3 taken together with the nitrogen atom to which they are attached form a ring having from 3 to 7 ring atoms;
(4) -C(=O)R^4, wherein R^4 is independently as defined in (20), (21), (22) or (23);
(5) -F, -Cl, -Br, -I;
(6) -CN;
(7) -NO_2;
(8) -OH;
(9) -OR^5, wherein R^5 is independently as defined in (20), (21), (22) or (23);
(10) -SH;
(11) -SR^6, wherein R^6 is independently as defined in (20), (21), (22) or (23);
(12) -OC(=O)R^7, wherein R^7 is independently as defined in (20), (21), (22) or (23);

(13) $-NR^8R^9$, wherein each of R^8 and R^9 is independently -H; or as defined in (20), (21), (22) or (23); or R^8 and R^9 taken together with the nitrogen atom to which they are attached form a ring having from 3 to 7 ring atoms;

(14) $-NR^{10}C(=O)R^{11}$, wherein R^{10} is independently -H; or as defined in (20), (21), (22) or (23); and R^{11} is independently -H, or as defined in (20), (21), (22) or (23);

(15) $-NR^{12}C(=O)NR^{13}R^{14}$ or $-NR^{12}C(=S)NR^{13}R^{14}$, wherein R^{12} is independently -H; or as defined in (20), (21), (22) or (23); and each of R^{13} and R^{14} is independently -H; or as defined in (20), (21), (22) or (23); or R^{13} and R^{14} taken together with the nitrogen atom to which they are attached form a ring having from 3 to 7 ring atoms;

(16) $-NR^{15}SO_2R^{16}$, wherein R^{15} is independently -H; or as defined in (20), (21), (22) or (23); and R^{16} is independently -H, or as defined in (20), (21), (22) or (23);

(17) $-SO_2R^{17}$, wherein R^{17} is independently as defined in (20), (21), (22) or (23);

(18) $-OSO_2R^{18}$, wherein R^{18} is independently as defined in (20), (21), (22) or (23);

(19) $-SO_2NR^{19}R^{20}$, wherein each of R^{19} and R^{20} is independently -H; or as defined in (20), (21), (22) or (23); or R^{19} and R^{20} taken together with the nitrogen atom to which they are attached form a ring having from 3 to 7 ring atoms;

(20) C_{5-20}aryl-C_{1-7}alkyl, for example, wherein C_{5-20}aryl is as defined in (21); unsubstituted or substituted with one or more groups as defined in (1) to (26);

(21) C_{5-20}aryl, including C_{6-20}carboaryl and C_{5-20}heteroaryl; unsubstituted or substituted with one or more groups as defined in (1) to (26);

(22) C_{3-20}heterocyclyl; unsubstituted or substituted with one or more groups as defined in (1) to (26);

(23) C_{1-7}alkyl, including:

unsaturated C_{1-7}alkyl, e.g., C_{2-7}alkenyl and C_{2-7}alkynyl;

cyclic C_{1-7}alkyl, e.g., C_{3-7}cycloalkyl C_{3-7}cycloalkenyl, C_{3-7}cycloalkynyl;

C_{1-7}alkyl substituted with one or more groups as defined in (1) to (22) and (24) to (26),

e.g., halo-C_{1-7}alkyl;

e.g., amino-C_{1-7}alkyl (e.g., $-(CH_2)_w$-amino, w is 1, 2, 3, or 4);

e.g., carboxy-C_{1-7}alkyl (e.g., $-(CH_2)_w$-COOH, w is 1, 2, 3, or 4);

e.g., hydroxy-C_{1-7}alkyl (e.g., $-(CH_2)_w$-OH, w is 1, 2, 3, or 4);

e.g., C_{1-7}alkoxy-C_{1-7}alkyl (e.g., $-(CH_2)_w$-O-C_{1-7}alkyl, w is 1, 2, 3, or 4);

(24) =O;

(25) $=NR^{21}$, wherein R^{21} is independently -H; or as defined in (20), (21), (22) or (23);

(26) =NOH.

In one embodiment, each of those substituents is independently selected from:

(1) -C(=O)OH;

(2) -C(=O)OMe, -C(=O)OEt, -C(=O)O(iPr), -C(=O)O(tBu); -C(=O)O(cPr);
-C(=O)OCH_2CH_2OH, -C(=O)OCH_2CH_2OMe, -C(=O)OCH_2CH_2OEt;
-C(=O)OPh, -C(=O)OCH_2Ph;

(3) -(C=O)NH_2, -(C=O)NMe_2, -(C=O)NEt_2, -(C=O)$N(iPr)_2$, -(C=O)$N(CH_2CH_2OH)_2$;
-(C=O)-morpholino, -(C=O)NHPh, -(C=O)$NHCH_2Ph$;

(4) -(C=O)Me, -(C=O)Et, -(C=O)(tBu), -(C=O)-cHex, -(C=O)Ph; -(C=O)CH_2Ph;

(5) -F, -Cl, -Br, -I;

(6) -CN;

(7) -NO_2;

(8) -OH;

(9) -OMe, -OEt, -O(iPr), -O(tBu), -OPh, -OCH_2Ph;
-OCF_3, -OCH_2CF_3;
-OCH_2CH_2OH, -OCH_2CH_2OMe, -OCH_2CH_2OEt;
-$OCH_2CH_2NH_2$, -$OCH_2CH_2NMe_2$, -$OCH_2CH_2N(iPr)_2$;
-OPh-Me, -OPh-OH, -OPh-OMe, -OPh-F, -OPh-Cl, -OPh-Br, -OPh-I;

(10) -SH;

(11) -SMe, -SEt, -SPh, -SCH_2Ph;

(12) -OC(=O)Me, -OC(=O)Et, -OC(=O)(iPr), -OC(=O)(tBu); -OC(=O)(cPr);
-OC(=O)CH_2CH_2OH, -OC(=O)CH_2CH_2OMe, -OC(=O)CH_2CH_2OEt;
-OC(=O)Ph, -OC(=O)CH_2Ph;

(13) -NH_2, -NHMe, -NHEt, -NH(iPr), -NMe_2, -NEt_2, -$N(iPr)_2$, -$N(CH_2CH_2OH)_2$;
-NHPh, -$NHCH_2Ph$; piperidino, piperazino, morpholino;

(14) -NH(C=O)Me, -NH(C=O)Et, -NH(C=O)Ph, -NHC(=O)CH_2Ph;
-NMe(C=O)Me, -NMe(C=O)Et, -NMe(C=O)Ph, -NMeC(=O)CH_2Ph;

(15) -NH(C=O)NH_2, -NH(C=O)NHMe, -NH(C=O)NHEt, -NH(C=O)NPh,
-NH(C=O)$NHCH_2Ph$; -NH(C=S)NH_2, -NH(C=S)NHMe, -NH(C=S)NHEt,
-NH(C=S)NPh, -NH(C=S)$NHCH_2Ph$;

(16) -$NHSO_2Me$, -$NHSO_2Et$, -$NHSO_2Ph$, -$NHSO_2PhMe$, -$NHSO_2CH_2Ph$;
-$NMeSO_2Me$, -$NMeSO_2Et$, -$NMeSO_2Ph$, -$NMeSO_2PhMe$, -$NMeSO_2CH_2Ph$;

(17) -SO_2Me, -SO_2CF_3, -SO_2Et, -SO_2Ph, -SO_2PhMe, -SO_2CH_2Ph;

(18) -OSO_2Me, -OSO_2CF_3, -OSO_2Et, -OSO_2Ph, -OSO_2PhMe, -OSO_2CH_2Ph;

(19) -SO_2NH_2, -SO_2NHMe, -SO_2NHEt, -SO_2NMe_2, -SO_2NEt_2, -SO_2-morpholino,
-SO_2NHPh, -SO_2NHCH_2Ph;

(20) -CH_2Ph, -CH_2Ph-Me, -CH_2Ph-OH, -CH_2Ph-F, -CH_2Ph-Cl;

(21) -Ph, -Ph-Me, -Ph-OH, -Ph-OMe, -Ph-F, -Ph-Cl, -Ph-Br, -Ph-I;
pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl; furanyl, thiophenyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, thiazolyl;

(22) pyrrolidinyl, piperidinyl, azepinyl, tetrahydropyranyl, morpholinyl, azetidinyl, piperazinyl, imidazolinyl, piperazinedionyl, and oxazolinonyl;

(23) -Me, -Et, -nPr, -iPr, -nBu, -iBu, -sBu, -tBu, -nPe;
-cPr, -cHex; $-CH=CH_2$, $-CH_2-CH=CH_2$;
$-CF_3$, $-CHF_2$, $-CH_2F$, $-CCl_3$, $-CBr_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, and $-CH_2CF_3$;
$-CH_2OH$, $-CH_2OMe$, $-CH_2OEt$, $-CH_2NH_2$, $-CH_2NMe_2$;
$-CH_2CH_2OH$, $-CH_2CH_2OMe$, $-CH_2CH_2OEt$, $-CH_2CH_2CH_2NH_2$, $-CH_2CH_2NMe_2$;
(24) =O;
(25) =NH, =NMe; =NEt;
(26) =NOH.

In one embodiment, each of those substituents is independently selected from:
(2) -C(=O)OMe;
(3) $-(C=O)NH_2$, $-(C=O)NMe_2$;
(4) -(C=O)Me, -(C=O)Et;
(5) -F, -Cl, -Br, -I;
(6) -CN;
(7) $-NO_2$;
(8) -OH;
(9) -OMe, -OEt;
(10) -SH;
(11) -SMe;
(13) $-NH_2$, $-NMe_2$, $-NEt_2$;
(21) -Ph;
(23) -Me, -Et, $-CF_3$.

Some Preferred Examples

In one embodiment, the compound is selected from: AM251; AM630; SR144528; "methyl"; "piperidyl"; "benzodioxo"; SR141716A; O-1184; JTE-907; AM281; cannabinol; cannabidiol; and Δ^9-THC.

In one embodiment, the compound is selected from: AM251; AM630; SR144528; SR141716A; O-1184; JTE-907; AM281; cannabinol; cannabidiol; and Δ^9-THC.

In one embodiment, the compound is selected from: AM251; AM630; SR144528; "methyl"; "piperidyl"; "benzodioxo"; SR141716A.

In one embodiment, the compound is selected from: SR141716A and AM251.

Chemical Terms

The term "carbo," "carbyl," "hydrocarbo," and "hydrocarbyl," as used herein, pertain to compounds and/or groups which have only carbon and hydrogen atoms (but see "carbocyclic" below).

The term "hetero," as used herein, pertains to compounds and/or groups which have at least one heteroatom, for example, multivalent heteroatoms (which are also suitable as ring heteroatoms) such as boron, silicon, nitrogen, phosphorus, oxygen, sulfur, and selenium (more commonly nitrogen, oxygen, and sulfur) and monovalent heteroatoms, such as fluorine, chlorine, bromine, and iodine.

The term "saturated," as used herein, pertains to compounds and/or groups which do not have any carbon-carbon double bonds or carbon-carbon triple bonds.

The term "unsaturated," as used herein, pertains to compounds and/or groups which have at least one carbon-carbon double bond or carbon-carbon triple bond.

The term "aliphatic," as used herein, pertains to compounds and/or groups which are linear or branched, but not cyclic (also known as "acyclic" or "open-chain" groups).

The term "ring," as used herein, pertains to a closed ring of from 3 to 10 covalently linked atoms, more preferably 3 to 8 covalently linked atoms, yet more preferably 5 to 6 covalently linked atoms. A ring may be an alicyclic ring or an aromatic ring. The term "alicyclic ring," as used herein, pertains to a ring which is not an aromatic ring.

The term "carbocyclic ring," as used herein, pertains to a ring wherein all of the ring atoms are carbon atoms.

The term "carboaromatic ring," as used herein, pertains to an aromatic ring wherein all of the ring atoms are carbon atoms.

The term "heterocyclic ring," as used herein, pertains to a ring wherein at least one of the ring atoms is a multivalent ring heteroatom, for example, nitrogen, phosphorus, silicon, oxygen, or sulfur, though more commonly nitrogen, oxygen, or sulfur. Preferably, the heterocyclic ring has from 1 to 4 heteroatoms.

The term "cyclic compound," as used herein, pertains to a compound which has at least one ring. The term "cyclyl," as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a ring atom of a cyclic compound.

Where a cyclic compound has two or more rings, they may be fused (e.g., as in naphthalene), bridged (e.g., as in norbornane), spiro (e.g., as in spiro[3.3]heptane), or a combination thereof. Cyclic compounds with one ring may be referred to as "monocyclic" or "mononuclear," whereas cyclic compounds with two or more rings may be referred to as "polycyclic" or "polynuclear."

The term "carbocyclic compound," as used herein, pertains to a cyclic compound which has only carbocyclic ring(s).

The term "heterocyclic compound," as used herein, pertains to a cyclic compound which has at least one heterocyclic ring.

The term "aromatic compound," as used herein, pertains to a cyclic compound which has at least one aromatic ring.

The term "carboaromatic compound," as used herein, pertains to a cyclic compound which has only carboaromatic ring(s).

The term "heteroaromatic compound," as used herein, pertains to a cyclic compound which has at least one heteroaromatic ring.

The term "monodentate substituents," as used herein, pertains to substituents which have one point of covalent attachment.

The term "monovalent monodentate substituents," as used herein, pertains to substituents which have one point of covalent attachment, via a single bond. Examples of such substituents include halo, hydroxy, and alkyl.

The term "multivalent monodentate substituents," as used herein, pertains to substituents which have one point of covalent attachment, but through a double bond or triple bond. Examples of such substituents include oxo, imino, alkylidene, and alklidyne.

The term "bidentate substituents," as used herein, pertains to substituents which have two points of covalent attachment, and which act as a linking group between two other moieties. Examples of such substituents include alkylene and arylene.

Substituents

The phrase "optionally substituted," as used herein, pertains to a parent group which may be unsubstituted or which may be substituted.

Unless otherwise specified, the term "substituted," as used herein, pertains to a parent group which bears one or more substituents. The term "substituent" is used herein in the conventional sense and refers to a chemical moiety which is covalently attached to, appended to, or if appropriate, fused to, a parent group. A wide variety of substituents are well known, and methods for their formation and introduction into a variety of parent groups are also well known.

The substituents are described in more detail below.

Alkyl: The term "alkyl," as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a carbon atom of a hydrocarbon compound having from 1 to 20 carbon atoms (unless otherwise specified), which may be aliphatic or alicyclic, and which may be saturated, partially unsaturated, or fully unsaturated. Thus, the term "alkyl" includes the sub-classes alkenyl, alkynyl, cycloalkyl, etc., discussed below.

In this context, the prefixes (e.g., C_{1-4}, C_{1-7}, C_{1-20}, C_{2-7}, C_{3-7}, etc.) denote the number of carbon atoms, or range of number of carbon atoms. For example, the term "C_{1-4}alkyl," as used herein, pertains to an alkyl group having from 1 to 4 carbon atoms. Examples of groups of alkyl groups include C_{1-4}alkyl ("lower alkyl"), C_{1-7}alkyl, and C_{1-20}alkyl.

Examples of (unsubstituted) saturated alkyl groups include, but are not limited to, methyl (C_1), ethyl (C_2), propyl (C_3), butyl (C_4), pentyl (C_5), hexyl (C_6), heptyl (C_7), octyl (C_8), nonyl (C_9), decyl (C_{10}), undecyl (C_{11}), dodecyl (C_{12}), tridecyl (C_{13}), tetradecyl (C_{14}), pentadecyl (C_{15}), and eicodecyl (C_{20}).

Examples of (unsubstituted) saturated linear alkyl groups include, but are not limited to, methyl (C_1), ethyl (C_2), n-propyl (C_3), n-butyl (C_4), n-pentyl (amyl) (C_5), n-hexyl (C_6), and n-heptyl (C_7).

Examples of (unsubstituted) saturated branched alkyl groups include iso-propyl (C_3), iso-butyl (C_4), sec-butyl (C_4), tert-butyl (C_4), iso-pentyl (C_5), and neo-pentyl (C_5).

Cycloalkyl: The term "cycloalkyl," as used herein, pertains to an alkyl group which is also a cyclyl group; that is, a monovalent moiety obtained by removing a hydrogen atom from an alicyclic ring atom of a cyclic hydrocarbon (carbocyclic) compound, which moiety has from 3 to 20 ring atoms (unless otherwise specified). Preferably, each ring has from 3 to 7 ring atoms.

Examples of (unsubstituted) saturated cylcoalkyl groups include, but are not limited to, those derived from: cyclopropane (C_3), cyclobutane (C_4), cyclopentane (C_5), cyclohexane (C_6), cycloheptane (C_7), norbornane (C_7), norpinane (C_7), norcarane (C_7), adamantane (C_{10}), and decalin (decahydronaphthalene) (C_{10}).

Examples of (substituted) saturated cycloalkyl groups, which are also referred to herein as "alkyl-cycloalkyl" groups, include, but are not limited to, methylcyclopropyl, dimethylcyclopropyl, methylcyclobutyl, dimethylcyclobutyl, methylcyclopentyl, dimethylcyclopentyl, methylcyclohexyl, and dimethylcyclohexyl, menthane, thujane, carane, pinane, bornane, norcarane, and camphene.

Examples of (substituted) unsaturated cyclic alkenyl groups, which are also referred to herein as "alkyl-cycloalkenyl" groups, include, but are not limited to, methylcyclopropenyl, dimethylcyclopropenyl, methylcyclobutenyl, dimethylcyclobutenyl, methylcyclopentenyl, dimethylcyclopentenyl, methylcyclohexenyl, and dimethylcyclohexenyl.

Examples of (substituted) cycloalkyl groups, with one or more other rings fused to the parent cycloalkyl group, include, but are not limited to, those derived from: indene (C_9), indan (e.g., 2,3-dihydro-1H-indene) (C_9), tetraline (1,2,3,4-tetrahydronaphthalene (C_{10}), acenaphthene (C_{12}), fluorene (C_{13}), phenalene (C_{13}), acephenanthrene (C_{15}), aceanthrene (C_{16}). For example, 2H-inden-2-yl is a C_5cycloalkyl group with a substituent (phenyl) fused thereto.

Alkenyl: The term "alkenyl," as used herein, pertains to an alkyl group having one or more carbon-carbon double bonds. Examples of groups of alkenyl groups include C_{2-4}alkenyl, C_{2-7}alkenyl, C_{2-20}alkenyl.

Examples of (unsubstituted) unsaturated alkenyl groups include, but are not limited to, ethenyl (vinyl, -CH=CH_2), 1-propenyl (-CH=CH-CH_3), 2-propenyl (allyl, -CH-CH=CH_2), isopropenyl (-C(CH_3)=CH_2), butenyl (C_4), pentenyl (C_5), and hexenyl (C_6).

Examples of (unsubstituted) unsaturated cyclic alkenyl groups, which are also referred to herein as "cycloalkenyl" groups, include, but are not limited to, cyclopropenyl (C_3), cyclobutenyl (C_4), cyclopentenyl (C_5), and cyclohexenyl (C_6).

Alkynyl: The term "alkynyl," as used herein, pertains to an alkyl group having one or more carbon-carbon triple bonds. Examples of groups of alkynyl groups include C_{2-4}alkynyl, C_{2-7}alkynyl, C_{2-20}alkynyl.

Examples of (unsubstituted) unsaturated alkynyl groups include, but are not limited to, ethynyl (ethinyl, -C≡CH) and 2-propynyl (propargyl, -CH_2-C≡CH).

Alkylidene: The term "alkylidene," as used herein, pertains to a divalent monodentate moiety obtained by removing two hydrogen atoms from a carbon atom of a hydrocarbon compound having from 1 to 20 carbon atoms (unless otherwise specified), which may be aliphatic or alicyclic, or a combination thereof, and which may be saturated, partially unsaturated, or fully unsaturated. Examples of groups of alkylidene groups include C_{1-4}alkylidene, C_{1-7}alkylidene, C_{1-20}alkylidene.

Examples of alkylidene groups include, but are not limited to, methylidene (=CH_2), ethylidene (=CH-CH_3), vinylidene (=C=CH_2), and isopropylidene (=C(CH_3)$_2$). An example of a substituted alkylidene is benzylidene (=CH-Ph).

Alkylidyne: The term "alkylidyne," as used herein, pertains to a trivalent monodentate moiety obtained by removing three hydrogen atoms from a carbon atom of a hydrocarbon compound having from 1 to 20 carbon atoms (unless otherwise specified), which may be aliphatic or alicyclic, or a combination thereof, and which may be saturated, partially unsaturated, or fully unsaturated. Examples of groups of alkylidyne groups include C_{1-4}alkylidyne, C_{1-7}alkylidyne, C_{1-20}alkylidyne.

Examples of alkylidyne groups include, but are not limited to, methylidyne (≡CH) and ethylidyne (≡C-CH_3).

Carbocyclyl: The term "carbocyclyl," as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a ring atom of a carbocyclic compound, which moiety has from 3 to 20 ring atoms (unless otherwise specified). Preferably, each ring has from 3 to 7 ring atoms.

In this context, the prefixes (e.g., C_{3-20}, C_{3-7}, C_{5-6}, etc.) denote the number of ring atoms, or range of number of ring atoms. For example, the term "C_{5-6}carbocyclyl," as used herein,

pertains to a carbocyclyl group having 5 or 6 ring atoms. Examples of groups of carbocyclyl groups include C_{3-20}carbocyclyl, C_{3-10}carbocyclyl, C_{5-10}carbocyclyl, C_{3-7}carbocyclyl, and C_{5-7}carbocyclyl.

Examples of carbocyclic groups include, but are not limited to, those described above as cycloalkyl groups; and those described below as carboaryl groups.

Heterocyclyl: The term "heterocyclyl," as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a ring atom of a heterocyclic compound, which moiety has from 3 to 20 ring atoms (unless otherwise specified), of which from 1 to 10 are ring heteroatoms. Preferably, each ring has from 3 to 7 ring atoms, of which from 1 to 4 are ring heteroatoms.

In this context, the prefixes (e.g., C_{3-20}, C_{3-7}, C_{5-6}, etc.) denote the number of ring atoms, or range of number of ring atoms, whether carbon atoms or heteroatoms. For example, the term "C_{5-6}heterocyclyl," as used herein, pertains to a heterocyclyl group having 5 or 6 ring atoms. Examples of groups of heterocyclyl groups include C_{3-20}heterocyclyl, C_{3-7}heterocyclyl, C_{5-7}heterocyclyl, and C_{5-6}heterocyclyl.

Examples of (non-aromatic) monocyclic heterocyclyl groups include, but are not limited to, those derived from:

N_1: aziridine (C_3), azetidine (C_4), pyrrolidine (tetrahydropyrrole) (C_5), pyrroline (e.g., 3-pyrroline, 2,5-dihydropyrrole) (C_5), 2H-pyrrole or 3H-pyrrole (isopyrrole, isoazole) (C_5), piperidine (C_6), dihydropyridine (C_6), tetrahydropyridine (C_6), azepine (C_7);

O_1: oxirane (C_3), oxetane (C_4), oxolane (tetrahydrofuran) (C_5), oxole (dihydrofuran) (C_5), oxane (tetrahydropyran) (C_6), dihydropyran (C_6), pyran (C_6), oxepin (C_7);

S_1: thiirane (C_3), thietane (C_4), thiolane (tetrahydrothiophene) (C_5), thiane (tetrahydrothiopyran) (C_6), thiepane (C_7);

O_2: dioxolane (C_5), dioxane (C_6), and dioxepane (C_7);

O_3: trioxane (C_6);

N_2: imidazolidine (C_5), pyrazolidine (diazolidine) (C_5), imidazoline (C_5), pyrazoline (dihydropyrazole) (C_5), piperazine (C_6);

N_1O_1: tetrahydrooxazole (C_5), dihydrooxazole (C_5), tetrahydroisoxazole (C_5), dihydroisoxazole (C_5), morpholine (C_6), tetrahydrooxazine (C_6), dihydrooxazine (C_6), oxazine (C_6);

N_1S_1: thiazoline (C_5), thiazolidine (C_5), thiomorpholine (C_6);

N_2O_1: oxadiazine (C_6);

O_1S_1: oxathiole (C_5) and oxathiane (thioxane) (C_6); and,

$N_1O_1S_1$: oxathiazine (C_6).

Examples of substituted (non-aromatic) monocyclic heterocyclyl groups include saccharides, in cyclic form, for example, furanoses (C_5), such as arabinofuranose, lyxofuranose, ribofuranose, and xylofuranse, and pyranoses (C_6), such as allopyranose, altropyranose, glucopyranose, mannopyranose, gulopyranose, idopyranose, galactopyranose, and talopyranose.

Examples of heterocyclyl groups which are also heteroaryl groups are described below with aryl groups.

Aryl: The term "aryl," as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from an aromatic ring atom of an aromatic compound, which moiety has from 3 to 20 ring atoms (unless otherwise specified). Preferably, each ring has from 5 to 7 ring atoms.

In this context, the prefixes (e.g., C_{3-20}, C_{5-7}, C_{5-6}, etc.) denote the number of ring atoms, or range of number of ring atoms, whether carbon atoms or heteroatoms. For example, the term "C_{5-6}aryl," as used herein, pertains to an aryl group having 5 or 6 ring atoms. Examples of groups of aryl groups include C_{3-20}aryl, C_{3-12}aryl, C_{5-12}aryl, C_{5-7}aryl, and C_{5-6}aryl.

The ring atoms may be all carbon atoms, as in "carboaryl groups" (e.g., C_{5-20}carboaryl).

Examples of carboaryl groups include, but are not limited to, those derived from benzene (i.e., phenyl) (C_6), naphthalene (C_{10}), azulene (C_{10}), anthracene (C_{14}), phenanthrene (C_{14}), naphthacene (C_{18}), and pyrene (C_{16}).

Examples of aryl groups which comprise fused rings, at least one of which is an aromatic ring, include, but are not limited to, groups derived from indene (C_9), isoindene (C_9), and fluorene (C_{13}).

Alternatively, the ring atoms may include one or more heteroatoms, as in "heteroaryl groups" (e.g., C_{5-20}heteroaryl).

Examples of monocyclic heteroaryl groups include, but are not limited to, those derived from:

N_1: pyrrole (azole) (C_5), pyridine (azine) (C_6);
O_1: furan (oxole) (C_5);
S_1: thiophene (thiole) (C_5);
N_1O_1: oxazole (C_5), isoxazole (C_5), isoxazine (C_6);
N_2O_1: oxadiazole (furazan) (C_5);
N_3O_1: oxatriazole (C_5);
N_1S_1: thiazole (C_5), isothiazole (C_5);
N_2: imidazole (1,3-diazole) (C_5), pyrazole (1,2-diazole) (C_5), pyridazine (1,2-diazine) (C_6), pyrimidine (1,3-diazine) (C_6) (e.g., cytosine, thymine, uracil), pyrazine (1,4-diazine) (C_6);
N_3: triazole (C_5), triazine (C_6); and,
N_4: tetrazole (C_5).

Examples of heterocyclic groups (some of which are also heteroaryl groups) which comprise fused rings, include, but are not limited to:

C_9heterocyclic groups (with 2 fused rings) derived from benzofuran (O_1), isobenzofuran (O_1), indole (N_1), isoindole (N_1), indolizine (N_1), indoline (N_1), isoindoline (N_1), purine (N_4) (e.g., adenine, guanine), benzimidazole (N_2), indazole (N_2), benzoxazole (N_1O_1), benzisoxazole (N_1O_1), benzodioxole (O_2), benzofurazan (N_2O_1), benzotriazole (N_3), benzothiofuran (S_1), benzothiazole (N_1S_1), benzothiadiazole (N_2S);

C_{10}heterocyclic groups (with 2 fused rings) derived from chromene (O_1), isochromene (O_1), chroman (O_1), isochroman (O_1), benzodioxan (O_2), quinoline (N_1), isoquinoline (N_1), quinolizine (N_1), benzoxazine (N_1O_1), benzodiazine (N_2), pyridopyridine (N_2), quinoxaline (N_2), quinazoline (N_2), cinnoline (N_2), phthalazine (N_2), naphthyridine (N_2), pteridine (N_4);

C_{13}heterocyclic groups (with 3 fused rings) derived from carbazole (N_1), dibenzofuran (O_1), dibenzothiophene (S_1), carboline (N_2), perimidine (N_2), pyridoindole (N_2); and,

C_{14}heterocyclic groups (with 3 fused rings) derived from acridine (N_1), xanthene (O_1), thioxanthene (S_1), oxanthrene (O_2), phenoxathiin (O_1S_1), phenazine (N_2),

phenoxazine (N_1O_1), phenothiazine (N_1S_1), thianthrene (S_2), phenanthridine (N_1), phenanthroline (N_2), phenazine (N_2).

Heterocyclic groups (including heteroaryl groups) which have a nitrogen ring atom in the form of an -NH- group may be N-substituted, that is, as -NR-. For example, pyrrole may be N-methyl substituted, to give N-methypyrrole. Examples of N-substituents include, but are not limited to C_{1-7}alkyl, C_{3-20}heterocyclyl, C_{5-20}aryl, and acyl groups.

Heterocyclic groups (including heteroaryl groups) which have a nitrogen ring atom in the form of an -N= group may be substituted in the form of an N-oxide, that is, as -N(→O)= (also denoted $-N^+(\rightarrow O^-)=$). For example, quinoline may be substituted to give quinoline N-oxide; pyridine to give pyridine N-oxide; benzofurazan to give benzofurazan N-oxide (also known as benzofuroxan).

Cyclic groups may additionally bear one or more oxo (=O) groups on ring carbon atoms. Monocyclic examples of such groups include, but are not limited to, those derived from:
C_5: cyclopentanone, cyclopentenone, cyclopentadienone;
C_6: cyclohexanone, cyclohexenone, cyclohexadienone;
O_1: furanone (C_5), pyrone (C_6);
N_1: pyrrolidone (pyrrolidinone) (C_5), piperidinone (piperidone) (C_6), piperidinedione (C_6);
N_2: imidazolidone (imidazolidinone) (C_5), pyrazolone (pyrazolinone) (C_5), piperazinone (C_6), piperazinedione (C_6), pyridazinone (C_6), pyrimidinone (C_6) (e.g., cytosine), pyrimidinedione (C_6) (e.g., thymine, uracil), barbituric acid (C_6);
N_1S_1: thiazolone (C_5), isothiazolone (C_5);
N_1O_1: oxazolinone (C_5).

Polycyclic examples of such groups include, but are not limited to, those derived from:
C_9: indenedione;
C_{10}: tetralone, decalone;
C_{14}: anthrone, phenanthrone;
N_1: oxindole (C_9);
O_1: benzopyrone (e.g., coumarin, isocoumarin, chromone) (C_{10});
N_1O_1: benzoxazolinone (C_9), benzoxazolinone (C_{10});
N_2: quinazolinedione (C_{10});
N_4: purinone (C_9) (e.g., guanine).

Still more examples of cyclic groups which bear one or more oxo (=O) groups on ring carbon atoms include, but are not limited to, those derived from:

cyclic anhydrides (-C(=O)-O-C(=O)- in a ring), including but not limited to maleic anhydride (C_5), succinic anhydride (C_5), and glutaric anhydride (C_6);

cyclic carbonates (-O-C(=O)-O- in a ring), such as ethylene carbonate (C_5) and 1,2-propylene carbonate (C_5);

imides (-C(=O)-NR-C(=O)- in a ring), including but not limited to, succinimide (C_5), maleimide (C_5), phthalimide, and glutarimide (C_6);

lactones (cyclic esters, -O-C(=O)- in a ring), including, but not limited to, β-propiolactone, γ-butyrolactone, δ-valerolactone (2-piperidone), and ε-caprolactone;

lactams (cyclic amides, -NR-C(=O)- in a ring), including, but not limited to, β-propiolactam (C_4), γ-butyrolactam (2-pyrrolidone) (C_5), δ-valerolactam (C_6), and ε-caprolactam (C_7);

cyclic carbamates (-O-C(=O)-NR- in a ring), such as 2-oxazolidone (C_5);

cyclic ureas (-NR-C(=O)-NR- in a ring), such as 2-imidazolidone (C_5) and pyrimidine-2,4-dione (e.g., thymine, uracil) (C_6).

The above alkyl, alkylidene, alkylidyne, heterocyclyl, and aryl groups, whether alone or part of another substituent, may themselves optionally be substituted with one or more groups selected from themselves and the additional substituents listed below.

Hydrogen: -H. Note that if the substituent at a particular position is hydrogen, it may be convenient to refer to the compound as being "unsubstituted" at that position.

Halo: -F, -Cl, -Br, and -I.

Hydroxy: -OH.

Ether: -OR, wherein R is an ether substituent, for example, a C_{1-7}alkyl group (also referred to as a C_{1-7}alkoxy group, discussed below), a C_{3-20}heterocyclyl group (also referred to as a C_{3-20}heterocyclyloxy group), or a C_{5-20}aryl group (also referred to as a C_{5-20}aryloxy group), preferably a C_{1-7}alkyl group.

C_{1-7}alkoxy: -OR, wherein R is a C_{1-7}alkyl group. Examples of C_{1-7}alkoxy groups include, but are not limited to, -OMe (methoxy), -OEt (ethoxy), -O(nPr) (n-propoxy), -O(iPr) (isopropoxy), -O(nBu) (n-butoxy), -O(sBu) (sec-butoxy), -O(iBu) (isobutoxy), and -O(tBu) (tert-butoxy).

Acetal: -CH(OR^1)(OR^2), wherein R^1 and R^2 are independently acetal substituents, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group, or, in the case of a "cyclic" acetal group, R^1 and R^2, taken together with

the two oxygen atoms to which they are attached, and the carbon atoms to which they are attached, form a heterocyclic ring having from 4 to 8 ring atoms. Examples of acetal groups include, but are not limited to, $-CH(OMe)_2$, $-CH(OEt)_2$, and -CH(OMe)(OEt).

Hemiacetal: $-CH(OH)(OR^1)$, wherein R^1 is a hemiacetal substituent, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group. Examples of hemiacetal groups include, but are not limited to, -CH(OH)(OMe) and -CH(OH)(OEt).

Ketal: $-CR(OR^1)(OR^2)$, where R^1 and R^2 are as defined for acetals, and R is a ketal substituent other than hydrogen, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group. Examples ketal groups include, but are not limited to, $-C(Me)(OMe)_2$, $-C(Me)(OEt)_2$, -C(Me)(OMe)(OEt), $-C(Et)(OMe)_2$, $-C(Et)(OEt)_2$, and -C(Et)(OMe)(OEt).

Hemiketal: $-CR(OH)(OR^1)$, where R^1 is as defined for hemiacetals, and R is a hemiketal substituent other than hydrogen, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group. Examples of hemiacetal groups include, but are not limited to, -C(Me)(OH)(OMe), -C(Et)(OH)(OMe), -C(Me)(OH)(OEt), and -C(Et)(OH)(OEt).

Oxo (keto, -one): =O.

Thione (thioketone): =S.

Imino (imine): =NR, wherein R is an imino substituent, for example, hydrogen, C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably hydrogen or a C_{1-7}alkyl group. Examples of ester groups include, but are not limited to, =NH, =NMe, =NEt, and =NPh.

Formyl (carbaldehyde, carboxaldehyde): -C(=O)H.

Acyl (keto): -C(=O)R, wherein R is an acyl substituent, for example, a C_{1-7}alkyl group (also referred to as C_{1-7}alkylacyl or C_{1-7}alkanoyl), a C_{3-20}heterocyclyl group (also referred to as C_{3-20}heterocyclylacyl), or a C_{5-20}aryl group (also referred to as C_{5-20}arylacyl), preferably a C_{1-7}alkyl group. Examples of acyl groups include, but are not limited to, $-C(=O)CH_3$ (acetyl), $-C(=O)CH_2CH_3$ (propionyl), $-C(=O)C(CH_3)_3$ (t-butyryl), and -C(=O)Ph (benzoyl, phenone).

Acylhalide (haloformyl, halocarbonyl): -C(=O)X, wherein X is -F, -Cl, -Br, or -I, preferably -Cl, -Br, or -I.

Carboxy (carboxylic acid): -C(=O)OH.

Thiocarboxy (thiocarboxylic acid): -C(=S)SH.

Thiolocarboxy (thiolocarboxylic acid): -C(=O)SH.

Thionocarboxy (thionocarboxylic acid): -C(=S)OH.

Imidic acid: -C(=NH)OH.

Hydroxamic acid: -C(=NOH)OH.

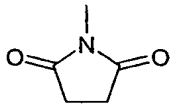
Ester (carboxylate, carboxylic acid ester, oxycarbonyl): -C(=O)OR, wherein R is an ester substituent, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group. Examples of ester groups include, but are not limited to, $-C(=O)OCH_3$, $-C(=O)OCH_2CH_3$, $-C(=O)OC(CH_3)_3$, and -C(=O)OPh.

Acyloxy (reverse ester): -OC(=O)R, wherein R is an acyloxy substituent, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group. Examples of acyloxy groups include, but are not limited to, $-OC(=O)CH_3$ (acetoxy), $-OC(=O)CH_2CH_3$, $-OC(=O)C(CH_3)_3$, -OC(=O)Ph, and $-OC(=O)CH_2Ph$.

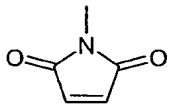
Oxycarboyloxy: -OC(=O)OR, wherein R is an ester substituent, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group. Examples of ester groups include, but are not limited to, $-OC(=O)OCH_3$, $-OC(=O)OCH_2CH_3$, $-OC(=O)OC(CH_3)_3$, and -OC(=O)OPh.

Amido (carbamoyl, carbamyl, aminocarbonyl, carboxamide): $-C(=O)NR^1R^2$, wherein R^1 and R^2 are independently amino substituents, as defined for amino groups. Examples of amido groups include, but are not limited to, $-C(=O)NH_2$, $-C(=O)NHCH_3$, $-C(=O)N(CH_3)_2$, $-C(=O)NHCH_2CH_3$, and $-C(=O)N(CH_2CH_3)_2$, as well as amido groups in which R^1 and R^2, together with the nitrogen atom to which they are attached, form a heterocyclic structure as in, for example, piperidinocarbonyl, morpholinocarbonyl, thiomorpholinocarbonyl, and piperazinocarbonyl.

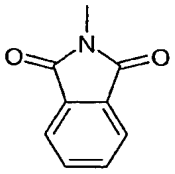
Acylamido (acylamino): -$NR^1C(=O)R^2$, wherein R^1 is an amide substituent, for example, hydrogen, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably hydrogen or a C_{1-7}alkyl group, and R^2 is an acyl substituent, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably hydrogen or a C_{1-7}alkyl group. Examples of acylamide groups include, but are not limited to, -$NHC(=O)CH_3$, -$NHC(=O)CH_2CH_3$, and -NHC(=O)Ph. R^1 and R^2 may together form a cyclic structure, as in, for example, succinimidyl, maleimidyl, and phthalimidyl:



succinimidyl



maleimidyl



phthalimidyl

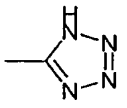
Aminocarbonyloxy: -$OC(=O)NR^1R^2$, wherein R^1 and R^2 are independently amino substituents, as defined for amino groups. Examples of aminocarbonyloxy groups include, but are not limited to, -$OC(=O)NH_2$, -OC(=O)NHMe, -$OC(=O)NMe_2$, and -$OC(=O)NEt_2$.

Thioamido (thiocarbamyl): -$C(=S)NR^1R^2$, wherein R^1 and R^2 are independently amino substituents, as defined for amino groups. Examples of amido groups include, but are not limited to, -$C(=S)NH_2$, -$C(=S)NHCH_3$, -$C(=S)N(CH_3)_2$, and -$C(=S)NHCH_2CH_3$.

Ureido: -$N(R^1)CONR^2R^3$ wherein R^2 and R^3 are independently amino substituents, as defined for amino groups, and R1 is a ureido substituent, for example, hydrogen, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably hydrogen or a C_{1-7}alkyl group. Examples of ureido groups include, but are not limited to, -$NHCONH_2$, -NHCONHMe, -NHCONHEt, -$NHCONMe_2$, -$NHCONEt_2$, -$NMeCONH_2$, -NMeCONHMe, -NMeCONHEt, -$NMeCONMe_2$, and -$NMeCONEt_2$.

Guanidino: -$NH-C(=NH)NH_2$.

Tetrazolyl: a five membered aromatic ring having four nitrogen atoms and one carbon atom,



Amino: -NR^1R^2, wherein R^1 and R^2 are independently amino substituents, for example, hydrogen, a C_{1-7}alkyl group (also referred to as C_{1-7}alkylamino or di-C_{1-7}alkylamino), a

C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably H or a C_{1-7}alkyl group, or, in the case of a "cyclic" amino group ("cycloamino"), R^1 and R^2, taken together with the nitrogen atom to which they are attached, form a heterocyclic ring having from 4 to 8 ring atoms. Amino groups may be primary ($-NH_2$), secondary ($-NHR^1$), or tertiary ($-NHR^1R^2$), and in cationic form, may be quaternary ($-^+NR^1R^2R^3$). Examples of amino groups include, but are not limited to, $-NH_2$, $-NHCH_3$, $-NHC(CH_3)_2$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, and -NHPh. Examples of cyclic amino groups include, but are not limited to, aziridino, azetidino, pyrrolidino, piperidino, piperazino, morpholino, and thiomorpholino.

Imino: =NR, wherein R is an imino substituent, for example, for example, hydrogen, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably H or a C_{1-7}alkyl group. Examples of imino groups include, but are not limited to, =NH, =NMe, and =NEt.

Amidine (amidino): $-C(=NR)NR_2$, wherein each R is an amidine substituent, for example, hydrogen, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably H or a C_{1-7}alkyl group. Examples of amidine groups include, but are not limited to, $-C(=NH)NH_2$, $-C(=NH)NMe_2$, and $-C(=NMe)NMe_2$.

Nitro: $-NO_2$.

Cyano (nitrile, carbonitrile): -CN.

Isocyano: -NC.

Cyanato: -OCN.

Isocyanato: -NCO.

Isothiocyano (isothiocyanato): -NCS.

Sulfhydryl (thiol, mercapto): -SH.

Thioether (sulfide): -SR, wherein R is a thioether substituent, for example, a C_{1-7}alkyl group (also referred to as a C_{1-7}alkylthio group), a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group. Examples of C_{1-7}alkylthio groups include, but are not limited to, $-SCH_3$ and $-SCH_2CH_3$.

Disulfide: -SS-R, wherein R is a disulfide substituent, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group (also referred to

herein as C_{1-7}alkyl disulfide). Examples of C_{1-7}alkyl disulfide groups include, but are not limited to, $-SSCH_3$ and $-SSCH_2CH_3$.

Sulfine (sulfinyl, sulfoxide): $-S(=O)R$, wherein R is a sulfine substituent, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group. Examples of sulfine groups include, but are not limited to, $-S(=O)CH_3$ and $-S(=O)CH_2CH_3$.

Sulfone (sulfonyl): $-S(=O)_2R$, wherein R is a sulfone substituent, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group, including, for example, a fluorinated or perfluorinated C_{1-7}alkyl group. Examples of sulfone groups include, but are not limited to, $-S(=O)_2CH_3$ (methanesulfonyl, mesyl), $-S(=O)_2CF_3$ (triflyl), $-S(=O)_2CH_2CH_3$ (esyl), $-S(=O)_2C_4F_9$ (nonaflyl), $-S(=O)_2CH_2CF_3$ (tresyl), $-S(=O)_2CH_2CH_2NH_2$ (tauryl), $-S(=O)_2Ph$ (phenylsulfonyl, besyl), 4-methylphenylsulfonyl (tosyl), 4-chlorophenylsulfonyl (closyl), 4-bromophenylsulfonyl (brosyl), 4-nitrophenyl (nosyl), 2-naphthalenesulfonate (napsyl), and 5-dimethylamino-naphthalen-1-ylsulfonate (dansyl).

Sulfinic acid (sulfino): $-S(=O)OH$, $-SO_2H$.

Sulfonic acid (sulfo): $-S(=O)_2OH$, $-SO_3H$.

Sulfinate (sulfinic acid ester): $-S(=O)OR$; wherein R is a sulfinate substituent, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group. Examples of sulfinate groups include, but are not limited to, $-S(=O)OCH_3$ (methoxysulfinyl; methyl sulfinate) and $-S(=O)OCH_2CH_3$ (ethoxysulfinyl; ethyl sulfinate).

Sulfonate (sulfonic acid ester): $-S(=O)_2OR$, wherein R is a sulfonate substituent, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group. Examples of sulfonate groups include, but are not limited to, $-S(=O)_2OCH_3$ (methoxysulfonyl; methyl sulfonate) and $-S(=O)_2OCH_2CH_3$ (ethoxysulfonyl; ethyl sulfonate).

Sulfinyloxy: $-OS(=O)R$, wherein R is a sulfinyloxy substituent, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group. Examples of sulfinyloxy groups include, but are not limited to, $-OS(=O)CH_3$ and $-OS(=O)CH_2CH_3$.

Sulfonyloxy: $-OS(=O)_2R$, wherein R is a sulfonyloxy substituent, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group.

Examples of sulfonyloxy groups include, but are not limited to, $-OS(=O)_2CH_3$ (mesylate) and $-OS(=O)_2CH_2CH_3$ (esylate).

Sulfate: $-OS(=O)_2OR$; wherein R is a sulfate substituent, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group. Examples of sulfate groups include, but are not limited to, $-OS(=O)_2OCH_3$ and $-SO(=O)_2OCH_2CH_3$.

Sulfamyl (sulfamoyl; sulfinic acid amide; sulfinamide): $-S(=O)NR^1R^2$, wherein R^1 and R^2 are independently amino substituents, as defined for amino groups. Examples of sulfamyl groups include, but are not limited to, $-S(=O)NH_2$, $-S(=O)NH(CH_3)$, $-S(=O)N(CH_3)_2$, $-S(=O)NH(CH_2CH_3)$, $-S(=O)N(CH_2CH_3)_2$, and $-S(=O)NHPh$.

Sulfonamido (sulfinamoyl; sulfonic acid amide; sulfonamide): $-S(=O)_2NR^1R^2$, wherein R^1 and R^2 are independently amino substituents, as defined for amino groups. Examples of sulfonamido groups include, but are not limited to, $-S(=O)_2NH_2$, $-S(=O)_2NH(CH_3)$, $-S(=O)_2N(CH_3)_2$, $-S(=O)_2NH(CH_2CH_3)$, $-S(=O)_2N(CH_2CH_3)_2$, and $-S(=O)_2NHPh$.

Sulfamino: $-NR^1S(=O)_2OH$, wherein R^1 is an amino substituent, as defined for amino groups. Examples of sulfamino groups include, but are not limited to, $-NHS(=O)_2OH$ and $-N(CH_3)S(=O)_2OH$.

Sulfonamino: $-NR^1S(=O)_2R$, wherein R^1 is an amino substituent, as defined for amino groups, and R is a sulfonamino substituent, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group. Examples of sulfonamino groups include, but are not limited to, $-NHS(=O)_2CH_3$ and $-N(CH_3)S(=O)_2C_6H_5$.

Sulfinamino: $-NR^1S(=O)R$, wherein R^1 is an amino substituent, as defined for amino groups, and R is a sulfinamino substituent, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group. Examples of sulfinamino groups include, but are not limited to, $-NHS(=O)CH_3$ and $-N(CH_3)S(=O)C_6H_5$.

In many cases, substituents may themselves be substituted. For example, a C_{1-7}alkyl group may be substituted with, for example, hydroxy (also referred to as a C_{1-7}hydroxyalkyl group), C_{1-7}alkoxy (also referred to as a C_{1-7}alkoxyalkyl group), amino (also referred to as a C_{1-7}aminoalkyl group), halo (also referred to as a C_{1-7}haloalkyl group), carboxy (also referred to as a C_{1-7}carboxyalkyl group), and C_{5-20}aryl (also referred to as a C_{5-20}aryl-C_{1-7}alkyl group).

Similarly, a C_{5-20}aryl group may be substituted with, for example, hydroxy (also referred to as a C_{5-20}hydroxyaryl group), halo (also referred to as a C_{5-20}haloaryl group), amino (also referred to as a C_{5-20}aminoaryl group, e.g., as in aniline), C_{1-7}alkyl (also referred to as a C_{1-7}alkyl-C_{5-20}aryl group, e.g., as in toluene), and C_{1-7}alkoxy (also referred to as a C_{1-7}alkoxy-C_{5-20}aryl group, e.g., as in anisole).

These and other specific examples of such substituted-substituents are described below.

Hydroxy-C_{1-7}alkyl: The term " hydroxy-C_{1-7}alkyl," as used herein, pertains to a C_{1-7}alkyl group in which at least one hydrogen atom (e.g., 1, 2, 3) has been replaced with a hydroxy group. Examples of such groups include, but are not limited to, $-CH_2OH$, $-CH_2CH_2OH$, and $-CH(OH)CH_2OH$.

Halo-C_{1-7}alkyl group: The term " halo-C_{1-7}alkyl," as used herein, pertains to a C_{1-7}alkyl group in which at least one hydrogen atom (e.g., 1, 2, 3) has been replaced with a halogen atom (e.g., F, Cl, Br, I). If more than one hydrogen atom has been replaced with a halogen atom, the halogen atoms may independently be the same or different. Every hydrogen atom may be replaced with a halogen atom, in which case the group may conveniently be referred to as a C_{1-7}perhaloalkyl group." Examples of such groups include, but are not limited to, $-CF_3$, $-CHF_2$, $-CH_2F$, $-CCl_3$, $-CBr_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, and $-CH_2CF_3$.

Amino-C_{1-7}alkyl: The term " amino-C_{1-7}alkyl," as used herein, pertains to a C_{1-7}alkyl group in which at least one hydrogen atom (e.g., 1, 2, 3) has been replaced with an amino group. Examples of such groups include, but are not limited to, $-CH_2NH_2$, $-CH_2CH_2NH_2$, and $-CH_2CH_2N(CH_3)_2$.

Carboxy-C_{1-7}alkyl: The term "carboxy-C_{1-7}alkyl," as used herein, pertains to a C_{1-7}alkyl group in which at least one hydrogen atom (e.g., 1, 2, 3) has been replaced with a carboxy group. Examples of such groups include, but are not limited to, $-CH_2COOH$ and $-CH_2CH_2COOH$.

C_{1-7}alkoxy-C_{1-7}alkyl: The term "C_{1-7}alkoxy-C_{1-7}alkyl," as used herein, pertains to a C_{1-7}alkyl group in which at least one hydrogen atom (e.g., 1, 2, 3) has been replaced with a C_{1-7}alkoxy group. Examples of such groups include, but are not limited to, $-CH_2OCH_3$, $-CH_2CH_2OCH_3$, and ,$-CH_2CH_2OCH_2CH_3$.

C_{5-20}aryl-C_{1-7}alkyl: The term "C_{5-20}aryl-C_{1-7}alkyl," as used herein, pertains to a C_{1-7}alkyl group in which at least one hydrogen atom (e.g., 1, 2, 3) has been replaced with a C_{5-}

$_{20}$aryl group. Examples of such groups include, but are not limited to, benzyl (phenylmethyl, $PhCH_2$-), benzhydryl (Ph_2CH-), trityl (triphenylmethyl, Ph_3C-), phenethyl (phenylethyl, Ph-CH_2CH_2-), styryl (Ph-CH=CH-), cinnamyl (Ph-CH=CH-CH_2-).

Hydroxy-C_{5-20}aryl: The term " hydroxy-C_{5-20}aryl," as used herein, pertains to a C_{5-20}aryl group in which at least one hydrogen atom (e.g., 1, 2, 3) has been substituted with an hydroxy group. Examples of such groups include, but are not limited to, those derived from: phenol, naphthol, pyrocatechol, resorcinol, hydroquinone, pyrogallol, phloroglucinol.

Halo-C_{5-20}aryl: The term "halo-C_{5-20}aryl," as used herein, pertains to a C_{5-20}aryl group in which at least one hydrogen atom (e.g., 1, 2, 3) has been substituted with a halo (e.g., F, Cl, Br, I) group. Examples of such groups include, but are not limited to, halophenyl (e.g., fluorophenyl, chlorophenyl, bromophenyl, or iodophenyl, whether ortho-, meta-, or para-substituted), dihalophenyl, trihalophenyl, tetrahalophenyl, and pentahalophenyl.

C_{1-7}alkyl-C_{5-20}aryl: The term "C_{1-7}alkyl-C_{5-20}aryl," as used herein, pertains to a C_{5-20}aryl group in which at least one hydrogen atom (e.g., 1, 2, 3) has been substituted with a C_{1-7}alkyl group. Examples of such groups include, but are not limited to, tolyl (from toluene), xylyl (from xylene), mesityl (from mesitylene), and cumenyl (or cumyl, from cumene), and duryl (from durene).

Hydroxy-C_{1-7}alkoxy: -OR, wherein R is a hydroxy-C_{1-7}alkyl group. Examples of hydroxy-C_{1-7}alkoxy groups include, but are not limited to, $-OCH_2OH$, $-OCH_2CH_2OH$, and $-OCH_2CH_2CH_2OH$.

Halo-C_{1-7}alkoxy: -OR, wherein R is a halo-C_{1-7}alkyl group. Examples of halo-C_{1-7}alkoxy groups include, but are not limited to, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, $-OCCl_3$, $-OCBr_3$, $-OCH_2CH_2F$, $-OCH_2CHF_2$, and $-OCH_2CF_3$.

Carboxy-C_{1-7}alkoxy: -OR, wherein R is a carboxy-C_{1-7}alkyl group. Examples of carboxy-C_{1-7}alkoxy groups include, but are not limited to, $-OCH_2COOH$, $-OCH_2CH_2COOH$, and $-OCH_2CH_2CH_2COOH$.

C_{1-7}alkoxy-C_{1-7}alkoxy: -OR, wherein R is a C_{1-7}alkoxy-C_{1-7}alkyl group. Examples of C_{1-7}alkoxy-C_{1-7}alkoxy groups include, but are not limited to, $-OCH_2OCH_3$, $-OCH_2CH_2OCH_3$, and $-OCH_2CH_2OCH_2CH_3$.

C_{5-20}aryl-C_{1-7}alkoxy: -OR, wherein R is a C_{5-20}aryl-C_{1-7}alkyl group. Examples of such groups include, but are not limited to, benzyloxy, benzhydryloxy, trityloxy, phenethoxy, styryloxy, and cimmamyloxy.

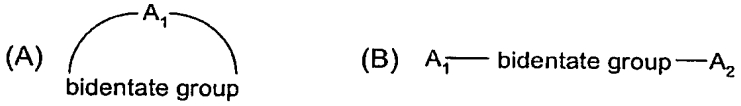
C_{1-7}alkyl-C_{5-20}aryloxy: -OR, wherein R is a C_{1-7}alkyl-C_{5-20}aryl group. Examples of such groups include, but are not limited to, tolyloxy, xylyloxy, mesityloxy, cumenyloxy, and duryloxy.

Amino-C_{1-7}alkyl-amino: The term "amino-C_{1-7}alkyl-amino," as used herein, pertains to an amino group, $-NR^1R^2$, in which one of the substituents, R^1 or R^2, is itself a amino-C_{1-7}alkyl group ($-C_{1-7}$alkyl-NR^3R^4). The amino-C_{1-7}alkylamino group may be represented, for example, by the formula $-NR^1-C_{1-7}$alkyl-NR^3R^4. Examples of such groups include, but are not limited to, groups of the formula $-NR^1(CH_2)_nNR^1R^2$, where n is 1 to 6 (for example, $-NHCH_2NH_2$, $-NH(CH_2)_2NH_2$, $-NH(CH_2)_3NH_2$, $-NH(CH_2)_4NH_2$, $-NH(CH_2)_5NH_2$, $-NH(CH_2)_6NH_2$), $-NHCH_2NH(Me)$, $-NH(CH_2)_2NH(Me)$, $-NH(CH_2)_3NH(Me)$, $-NH(CH_2)_4NH(Me)$, $-NH(CH_2)_5NH(Me)$, $-NH(CH_2)_6NH(Me)$, $-NHCH_2NH(Et)$, $-NH(CH_2)_2NH(Et)$, $-NH(CH_2)_3NH(Et)$, $-NH(CH_2)_4NH(Et)$, $-NH(CH_2)_5NH(Et)$, and $-NH(CH_2)_6NH(Et)$.

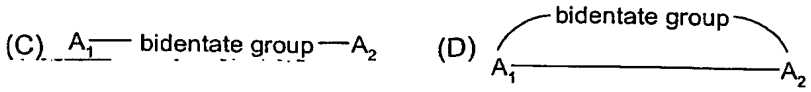
Bidentate Substituents

The term "bidentate substituents," as used herein, pertains to substituents which have two points of covalent attachment, and which act as a linking group between two other moieties.

In some cases (A), a bidentate substituent is covalently bound to a single atom. In some cases (B), a bidentate substituent is covalently bound to two different atoms, and so serves as a linking group therebetween.



Within (B), in some cases (C), a bidentate substituent is covalently bound to two different atoms, which themselves are not otherwise covalently linked (directly, or via intermediate groups). In some cases (D), a bidentate substituent is covalently bound to two different atoms, which themselves are already covalently linked (directly, or via intermediate groups); in such cases, a cyclic structure results. In some cases, the bidentate group is covalently bound to vicinal atoms, that is, adjacent atoms, in the parent group.



In some cases (A and D), the bidentate group, together with the atom(s) to which it is attached (and any intervening atoms, if present) form an additional cyclic structure. In this way, the bidentate substituent may give rise to a cyclic or polycyclic (e.g., fused, bridged, spiro) structure, which may be aromatic.

Examples of bidentate groups include, but are not limited to, C_{1-7}alkylene groups, C_{3-20}heterocyclylene groups, and C_{5-20}arylene groups, and substituted forms thereof.

Includes Other Forms

Unless otherwise specified, included in the above are the well known ionic, salt, solvate, and protected forms of these substituents. For example, a reference to carboxylic acid (-COOH) also includes the anionic (carboxylate) form ($-COO^-$), a salt or solvate thereof, as well as conventional protected forms. Similarly, a reference to an amino group includes the protonated form ($-N^+HR^1R^2$), a salt or solvate of the amino group, for example, a hydrochloride salt, as well as conventional protected forms of an amino group. Similarly, a reference to a hydroxyl group also includes the anionic form ($-O^-$), a salt or solvate thereof, as well as conventional protected forms.

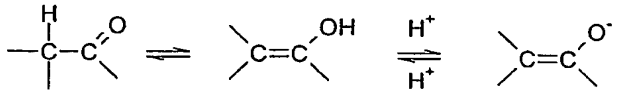
Isomers, Salts, Solvates, Protected Forms, and Prodrugs

Certain compounds may exist in one or more particular geometric, optical, enantiomeric, diasteriomeric, epimeric, atropic, stereoisomeric, tautomeric, conformational, or anomeric forms, including but not limited to, cis- and trans-forms; E- and Z-forms; c-, t-, and r-forms; endo- and exo-forms; R-, S-, and meso-forms; D- and L-forms; d- and l-forms; (+) and (-) forms; keto-, enol-, and enolate-forms; syn- and anti-forms; synclinal- and anticlinal-forms; α- and β-forms; axial and equatorial forms; boat-, chair-, twist-, envelope-, and halfchair-forms; and combinations thereof, hereinafter collectively referred to as "isomers" (or "isomeric forms").

Note that, except as discussed below for tautomeric forms, specifically excluded from the term "isomers," as used herein, are structural (or constitutional) isomers (i.e., isomers which differ in the connections between atoms rather than merely by the position of atoms in space). For example, a reference to a methoxy group, $-OCH_3$, is not to be construed as a reference to its structural isomer, a hydroxymethyl group, $-CH_2OH$. Similarly, a

reference to ortho-chlorophenyl is not to be construed as a reference to its structural isomer, meta-chlorophenyl. However, a reference to a class of structures may well include structurally isomeric forms falling within that class (e.g., C_{1-7}alkyl includes n-propyl and iso-propyl; butyl includes n-, iso-, sec-, and tert-butyl; methoxyphenyl includes ortho-, meta-, and para-methoxyphenyl).

The above exclusion does not pertain to tautomeric forms, for example, keto-, enol-, and enolate-forms, as in, for example, the following tautomeric pairs: keto/enol (illustrated below), imine/enamine, amide/imino alcohol, amidine/amidine, nitroso/oxime, thioketone/enethiol, N-nitroso/hyroxyazo, and nitro/aci-nitro.



keto enol enolate

Note that specifically included in the term "isomer" are compounds with one or more isotopic substitutions. For example, H may be in any isotopic form, including ^{1}H, ^{2}H (D), and ^{3}H (T); C may be in any isotopic form, including ^{12}C, ^{13}C, and ^{14}C; O may be in any isotopic form, including ^{16}O and ^{18}O; and the like.

Unless otherwise specified, a reference to a particular compound includes all such isomeric forms, including (wholly or partially) racemic and other mixtures thereof. Methods for the preparation (e.g., asymmetric synthesis) and separation (e.g., fractional crystallisation and chromatographic means) of such isomeric forms are either known in the art or are readily obtained by adapting the methods taught herein, or known methods, in a known manner.

Unless otherwise specified, a reference to a particular compound also includes ionic, salt, solvate, and protected forms of thereof, for example, as discussed below.

It may be convenient or desirable to prepare, purify, and/or handle a corresponding salt of the active compound, for example, a pharmaceutically-acceptable salt. Examples of pharmaceutically acceptable salts are discussed in Berge et al., 1977, "Pharmaceutically Acceptable Salts," J. Pharm. Sci., Vol. 66, pp. 1-19.

For example, if the compound is anionic, or has a functional group which may be anionic (e.g., -COOH may be $-COO^{-}$), then a salt may be formed with a suitable cation. Examples of suitable inorganic cations include, but are not limited to, alkali metal ions such as Na^{+} and K^{+}, alkaline earth cations such as Ca^{2+} and Mg^{2+}, and other cations such as Al^{+3}.

Examples of suitable organic cations include, but are not limited to, ammonium ion (i.e., NH_4^+) and substituted ammonium ions (e.g., NH_3R^+, $NH_2R_2^+$, NHR_3^+, NR_4^+). Examples of some suitable substituted ammonium ions are those derived from: ethylamine, diethylamine, dicyclohexylamine, triethylamine, butylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine, benzylamine, phenylbenzylamine, choline, meglumine, and tromethamine, as well as amino acids, such as lysine and arginine. An example of a common quaternary ammonium ion is $N(CH_3)_4^+$.

If the compound is cationic, or has a functional group which may be cationic (e.g., $-NH_2$ may be $-NH_3^+$), then a salt may be formed with a suitable anion. Examples of suitable inorganic anions include, but are not limited to, those derived from the following inorganic acids: hydrochloric, hydrobromic, hydroiodic, sulfuric, sulfurous, nitric, nitrous, phosphoric, and phosphorous.

Examples of suitable organic anions include, but are not limited to, those derived from the following organic acids: 2-acetyoxybenzoic, acetic, ascorbic, aspartic, benzoic, camphorsulfonic, cinnamic, citric, edetic, ethanedisulfonic, ethanesulfonic, fumaric, glucheptonic, gluconic, glutamic, glycolic, hydroxymaleic, hydroxynaphthalene carboxylic, isethionic, lactic, lactobionic, lauric, maleic, malic, methanesulfonic, mucic, oleic, oxalic, palmitic, pamoic, pantothenic, phenylacetic, phenylsulfonic, propionic, pyruvic, salicylic, stearic, succinic, sulfanilic, tartaric, toluenesulfonic, and valeric. Examples of suitable polymeric organic anions include, but are not limited to, those derived from the following polymeric acids: tannic acid, carboxymethyl cellulose.

It may be convenient or desirable to prepare, purify, and/or handle a corresponding solvate of the active compound. The term "solvate" is used herein in the conventional sense to refer to a complex of solute (e.g., active compound, salt of active compound) and solvent. If the solvent is water, the solvate may be conveniently referred to as a hydrate, for example, a mono-hydrate, a di-hydrate, a tri-hydrate, etc.

It may be convenient or desirable to prepare, purify, and/or handle the active compound in a chemically protected form. The term "chemically protected form" is used herein in the conventional chemical sense and pertains to a compound in which one or more reactive functional groups are protected from undesirable chemical reactions under specified conditions (e.g., pH, temperature, radiation, solvent, and the like). In practice, well known chemical methods are employed to reversibly render unreactive a functional group, which otherwise would be reactive, under specified conditions. In a chemically protected form, one or more reactive functional groups are in the form of a protected or protecting group (also known as a masked or masking group or a blocked or blocking group). By

protecting a reactive functional group, reactions involving other unprotected reactive functional groups can be performed, without affecting the protected group; the protecting group may be removed, usually in a subsequent step, without substantially affecting the remainder of the molecule. See, for example, Protective Groups in Organic Synthesis (T. Green and P. Wuts; 3rd Edition; John Wiley and Sons, 1999).

A wide variety of such "protecting," "blocking," or "masking" methods are widely used and well known in organic synthesis. For example, a compound which has two nonequivalent reactive functional groups, both of which would be reactive under specified conditions, may be derivatized to render one of the functional groups "protected," and therefore unreactive, under the specified conditions; so protected, the compound may be used as a reactant which has effectively only one reactive functional group. After the desired reaction (involving the other functional group) is complete, the protected group may be "deprotected" to return it to its original functionality.

For example, a hydroxy group may be protected as an ether (-OR) or an ester (-OC(=O)R), for example, as: a t-butyl ether; a benzyl, benzhydryl (diphenylmethyl), or trityl (triphenylmethyl) ether; a trimethylsilyl or t-butyldimethylsilyl ether; or an acetyl ester (-OC(=O)CH_3, -OAc).

For example, an aldehyde or ketone group may be protected as an acetal (R-CH$(OR)_2$) or ketal ($R_2C(OR)_2$), respectively, in which the carbonyl group (>C=O) is converted to a diether (>$C(OR)_2$), by reaction with, for example, a primary alcohol. The aldehyde or ketone group is readily regenerated by hydrolysis using a large excess of water in the presence of acid.

For example, an amine group may be protected, for example, as an amide (-NRCO-R) or a urethane (-NRCO-OR), for example, as: a methyl amide (-NHCO-CH_3); a benzyloxy amide (-NHCO-$OCH_2C_6H_5$, -NH-Cbz); as a t-butoxy amide (-NHCO-$OC(CH_3)_3$, -NH-Boc); a 2-biphenyl-2-propoxy amide (-NHCO-$OC(CH_3)_2C_6H_4C_6H_5$, -NH-Bpoc), as a 9-fluorenylmethoxy amide (-NH-Fmoc), as a 6-nitroveratryloxy amide (-NH-Nvoc), as a 2-trimethylsilylethyloxy amide (-NH-Teoc), as a 2,2,2-trichloroethyloxy amide (-NH-Troc), as an allyloxy amide (-NH-Alloc), as a 2(-phenylsulphonyl)ethyloxy amide (-NH-Psec); or, in suitable cases (e.g., cyclic amines), as a nitroxide radical (>N-O•).

For example, a carboxylic acid group may be protected as an ester for example, as: an C_{1-7}alkyl ester (e.g., a methyl ester; a t-butyl ester); a C_{1-7}haloalkyl ester (e.g., a C_{1-7}trihaloalkyl ester); a triC_{1-7}alkylsilyl-C_{1-7}alkyl ester; or a C_{5-20}aryl-C_{1-7}alkyl ester (e.g., a benzyl ester; a nitrobenzyl ester); or as an amide, for example, as a methyl amide.

For example, a thiol group may be protected as a thioether (-SR), for example, as: a benzyl thioether; an acetamidomethyl ether ($-S-CH_2NHC(=O)CH_3$).

It may be convenient or desirable to prepare, purify, and/or handle the active compound in the form of a prodrug. The term "prodrug," as used herein, pertains to a compound which, when metabolised (e.g., in vivo), yields the desired active compound. Typically, the prodrug is inactive, or less active than the active compound, but may provide advantageous handling, administration, or metabolic properties.

For example, some prodrugs are esters of the active compound (e.g., a physiologically acceptable metabolically labile ester). During metabolism, the ester group (-C(=O)OR) is cleaved to yield the active drug. Such esters may be formed by esterification, for example, of any of the carboxylic acid groups (-C(=O)OH) in the parent compound, with, where appropriate, prior protection of any other reactive groups present in the parent compound, followed by deprotection if required.

Examples of such metabolically labile esters include those of the formula -C(=O)OR wherein R is:

C_{1-7}alkyl (e.g., -Me, -Et, -nPr, -iPr, -nBu, -sBu, -iBu, -tBu);
C_{1-7}aminoalkyl (e.g., aminoethyl; 2-(N,N-diethylamino)ethyl; 2-(4-morpholino)ethyl); and
acyloxy-C_{1-7}alkyl
(e.g., acyloxymethyl;
acyloxyethyl;
pivaloyloxymethyl;
acetoxymethyl;
1-acetoxyethyl;
1-(1-methoxy-1-methyl)ethyl-carbonxyloxyethyl;
1-(benzoyloxy)ethyl; isopropoxy-carbonyloxymethyl;
1-isopropoxy-carbonyloxyethyl; cyclohexyl-carbonyloxymethyl;
1-cyclohexyl-carbonyloxyethyl;
cyclohexyloxy-carbonyloxymethyl;
1-cyclohexyloxy-carbonyloxyethyl;
(4-tetrahydropyranyloxy) carbonyloxymethyl;
1-(4-tetrahydropyranyloxy)carbonyloxyethyl;
(4-tetrahydropyranyl)carbonyloxymethyl; and
1-(4-tetrahydropyranyl)carbonyloxyethyl).

Also, some prodrugs are activated enzymatically to yield the active compound, or a compound which, upon further chemical reaction, yields the active compound (for example, as in ADEPT, GDEPT, LIDEPT, etc.). For example, the prodrug may be a sugar derivative or other glycoside conjugate, or may be an amino acid ester derivative.

Acronyms

For convenience, many chemical moieties are represented using well known abbreviations, including but not limited to, methyl (Me), ethyl (Et), n-propyl (nPr), iso-propyl (iPr), n-butyl (nBu), sec-butyl (sBu), iso-butyl (iBu), tert-butyl (tBu), n-hexyl (nHex), cyclohexyl (cHex), phenyl (Ph), biphenyl (biPh), benzyl (Bn), naphthyl (naph), methoxy (MeO), ethoxy (EtO), benzoyl (Bz), and acetyl (Ac).

Uses

The present invention pertains to cannabinoid receptor inverse agonists and cannabinoid receptor neutral antagonists , as described herein, which inhibit osteoclasts, for example, inhibit of the survival, formation, and/or activity of osteoclasts, and/or which inhibit bone resorption. Therefore, the compounds may also be referred to as "osteoclast inhibitors" and/or "bone resorption inhibitors."

One of ordinary skill in the art is readily able to determine whether or not a candidate compound inhibits the survival, formation, and/or activity of osteoclasts and/or inhibits bone resorption. For example, suitable methods which may conveniently be used in order to assess the inhibitory effects offered by a particular compound are described in the examples below.

Use in Methods of Inhibition

One aspect of the invention pertains to a method of inhibiting osteoclast survival, formation, and activity, *in vitro* or *in vivo*, comprising contacting an osteoclast with an effective amount of a cannabinoid receptor inverse agonist or a cannabinoid receptor neutral antagonist, as described herein.

One aspect of the invention pertains to a method of inhibiting bone resorption, *in vitro* or *in vivo*, comprising contacting cells in the bone microenvironment with a therapeutically-effective amount of a cannabinoid receptor inverse agonist or a cannabinoid receptor neutral antagonist, as described herein.

The term "cells in the bone microenvironment," as used herein, pertains to cells such as osteoblasts, osteoclasts, osteocytes and bone marrow stromal cells, which are located in close proximity to bone (e.g., within one hundred micrometers of the bone surface).

Bone Disorders

The cannabinoid receptor inverse agonists and cannabinoid receptor neutral antagonists, as described herein, are useful in the treatment of bone disorders, for example, conditions mediated by osteoclasts (e.g., by increased osteoclast activity) (as "osteoclast inhibitors"), and/or conditions characterised by increased bone resorption (as "bone resorption inhibitors").

In one embodiment, the bone disorder is characterised by increased osteoclast activity.

In one embodiment, the bone disorder is characterised by increased bone resorption.

In one embodiment, the bone disorder is associated with a genetic predisposition, sex hormone deficiency, or ageing. For example, in one embodiment, the bone disorder is characterised by increased bone resorption, and is associated with a genetic predisposition, sex hormone deficiency, or ageing.

In one embodiment, the bone disorder is not associated with inflammation. For example, in one embodiment, the bone disorder is characterised by increased bone resorption, and is not associated with inflammation. For example, in one embodiment, the bone disorder is characterised by increased bone resorption; and is associated with a genetic predisposition, sex hormone deficiency, or ageing; and is not associated with inflammation.

For example, in one embodiment, the bone disorder is not associated with rheumatoid arthritis, ankylosing spondylitis, or inflammatory bowel disease. For example, in one embodiment, the bone disorder is characterised by increased bone resorption, and is not associated with rheumatoid arthritis, ankylosing spondylitis, or inflammatory bowel disease. For example, in one embodiment, the bone disorder is characterised by increased bone resorption; and is associated with a genetic predisposition, sex hormone deficiency, or ageing; and is not associated with rheumatoid arthritis, ankylosing spondylitis, or inflammatory bowel disease.

Examples of such bone disorders include, but are not limited to, the following:

diseases of the skeleton, including but not limited to, pathologically low bone mineral density, such as:

osteoporosis (including, e.g., steroid induced osteoporosis) (e.g., osteoporosis not associated with inflammation);

osteoarthritis;

Paget's disease of bone (osteitis deformans);

hypercalcaemia caused by conditions associated with increased bone resorption, including, but not limited to: vitamin D intoxication, primary or tertiary hyperparathyroidism, immobilisation, and sarcoidosis;

neoplasia of bones, both as a primary tumour and as metastases, including but not limited to, osteosarcoma and osteoma (Zheng et al., 1998, J. Cell Biochem., Vol. 70, p. 121) and cancer associated bone disease (e.g., hypercalcaemia of malignancy, bone metastases, osteolytic bone metastases, multiple myeloma, breast carcinoma).

In one embodiment, the bone disorder is osteoporosis (e.g., osteoporosis not associated with inflammation; e.g., osteoporosis associated with a genetic predisposition, sex hormone deficiency, or ageing), cancer associated bone disease, and Paget's disease of bone.

In one embodiment, the bone disorder is osteoporosis (e.g., osteoporosis not associated with inflammation and/or osteoporosis associated with a genetic predisposition, sex hormone deficiency, or ageing).

Use in Methods of Treatment

One aspect of the present invention pertains to a method of treating a bone disorder, as described herein, comprising administering to a patient in need of treatment thereof a therapeutically effective amount of a cannabinoid receptor inverse agonist or a cannabinoid receptor neutral antagonist, as described herein, preferably in the form of a pharmaceutical composition.

One aspect of the present invention pertains to a method for the treatment of a condition mediated by osteoclasts (e.g., increased osteoclast activity) and/or characterised by (e.g., increased) bone resorption, as described herein, comprising administering to a subject suffering from said condition a therapeutically-effective amount of a cannabinoid receptor inverse agonist or a cannabinoid receptor neutral antagonist, as described herein, preferably in the form of a pharmaceutical composition.

One aspect of the present invention pertains to a method for the treatment of a condition mediated by osteoclasts (e.g., increased osteoclast activity), as described herein, comprising administering to a subject suffering from said condition a therapeutically-effective amount of a cannabinoid receptor inverse agonist or a cannabinoid receptor neutral antagonist, as described herein, preferably in the form of a pharmaceutical composition.

One aspect of the present invention pertains to a method for the treatment of a condition characterised by (e.g., increased) bone resorption, as described herein, comprising administering to a subject suffering from said condition a therapeutically-effective amount of a cannabinoid receptor inverse agonist or a cannabinoid receptor neutral antagonist, as described herein, preferably in the form of a pharmaceutical composition.

One aspect of the present invention pertains to a method for the treatment of osteoporosis (e.g., osteoporosis not associated with inflammation; e.g., osteoporosis associated with a genetic predisposition, sex hormone deficiency, or ageing), cancer associated bone disease, or Paget's disease of bone, comprising administering to a subject suffering from said condition a therapeutically-effective amount of a cannabinoid receptor inverse agonist or a cannabinoid receptor neutral antagonist, as described herein, preferably in the form of a pharmaceutical composition.

Use in Methods of Therapy

One aspect of the present invention pertains to a cannabinoid receptor inverse agonist or a cannabinoid receptor neutral antagonist, as described herein, for use in a method of treatment of the human or animal body by therapy.

One aspect of the present invention pertains to a cannabinoid receptor inverse agonist or a cannabinoid receptor neutral antagonist, as described herein, for use in a method of treatment of a condition mediated by osteoclasts (e.g., increased osteoclast activity) and/or characterised by (e.g., increased) bone resorption, as described herein, of the human or animal body by therapy.

One aspect of the present invention pertains to a cannabinoid receptor inverse agonist or a cannabinoid receptor neutral antagonist, as described herein, for use in a method of treatment of a condition mediated by osteoclasts (e.g., increased osteoclast activity), as described herein, of the human or animal body by therapy.

One aspect of the present invention pertains to a cannabinoid receptor inverse agonist or a cannabinoid receptor neutral antagonist, as described herein, for use in a method of treatment of a condition characterised by (e.g., increased) bone resorption, as described herein, of the human or animal body by therapy.

One aspect of the present invention pertains to a cannabinoid receptor inverse agonist or a cannabinoid receptor neutral antagonist, as described herein, for use in a method of treatment of osteoporosis (e.g., osteoporosis not associated with inflammation; e.g., osteoporosis associated with a genetic predisposition, sex hormone deficiency, or ageing), cancer associated bone disease, and Paget's disease of bone, of the human or animal body by therapy.

Use in the Manufacture of Medicaments

One aspect of the present invention pertains to use of a cannabinoid receptor inverse agonist or a cannabinoid receptor neutral antagonist, as described herein, for the manufacture of a medicament for use in the treatment of a condition mediated by osteoclasts (e.g., increased osteoclast activity) and/or characterised by (e.g., increased) bone resorption, as described herein.

One aspect of the present invention pertains to use of a cannabinoid receptor inverse agonist or a cannabinoid receptor neutral antagonist, as described herein, for the manufacture of a medicament for use in the treatment of a condition mediated by osteoclasts (e.g., increased osteoclast activity), as described herein.

One aspect of the present invention pertains to use of a cannabinoid receptor inverse agonist or a cannabinoid receptor neutral antagonist, as described herein, for the manufacture of a medicament for use in the treatment of a condition characterised by (e.g., increased) bone resorption, as described herein.

One aspect of the present invention pertains to use of a cannabinoid receptor inverse agonist or a cannabinoid receptor neutral antagonist, as described herein, for the manufacture of a medicament for use in the treatment of osteoporosis (e.g., osteoporosis not associated with inflammation; e.g., osteoporosis associated with a genetic predisposition, sex hormone deficiency, or ageing), cancer associated bone disease, and Paget's disease of bone.

Treatment

The term "treatment," as used herein in the context of treating a condition, pertains generally to treatment and therapy, whether of a human or an animal (e.g., in veterinary applications), in which some desired therapeutic effect is achieved, for example, the inhibition of the progress of the condition, and includes a reduction in the rate of progress, a halt in the rate of progress, amelioration of the condition, and cure of the condition. Treatment as a prophylactic measure (i.e., prophylaxis, prevention) is also included.

The term "therapeutically-effective amount," as used herein, pertains to that amount of an active compound, or a material, composition or dosage from comprising an active compound, which is effective for producing some desired therapeutic effect, commensurate with a reasonable benefit/risk ratio, when administered in accordance with a desired treatment regimen.

The term "treatment" includes combination treatments and therapies, in which two or more treatments or therapies are combined, for example, sequentially or simultaneously. Examples of treatments and therapies include, but are not limited to, chemotherapy (the administration of active agents, including, e.g., drugs, antibodies (e.g., as in immunotherapy), prodrugs (e.g., as in photodynamic therapy, GDEPT, ADEPT, etc.); surgery; radiation therapy; and gene therapy.

Other Uses

Cannabinoid receptor inverse agonists and cannabinoid receptor neutral antagonists, as described herein, may also be used as cell culture additives to inhibit osteoclasts, for example, to inhibit the survival, formation, and/or activity of osteoclasts.

Cannabinoid receptor inverse agonists and cannabinoid receptor neutral antagonists, as described herein, may also be used as part of an *in vitro* assay, for example, in order to determine whether a candidate host is likely to benefit from treatment with the compound in question.

Cannabinoid receptor inverse agonists and cannabinoid receptor neutral antagonists, as described herein, may also be used as a standard, for example, in an assay, in order to identify other active compounds, other osteoclast inhibitors, other bone resorption inhibitors, etc.

Methods of Identifying Bone Disorder Therapeutic Agents

One aspect of the present invention pertains to a method of identifying a bone disorder therapeutic agent on the basis that it has one or more of the functional characteristics described herein (e.g., is a cannabinoid receptor inverse agonist or a cannabinoid receptor neutral antagonist; is a CB1 or CB2 inverse agonist; etc.).

For example, one aspect of the present invention pertains to a method of identifying a bone disorder therapeutic agent on the basis that it is a cannabinoid receptor inverse agonist or a cannabinoid receptor neutral antagonist and has a cannabinoid receptor inhibition constant (Ki) of 10 μM or less, as described herein.

In one embodiment, the method further comprises the step of testing, demonstrating, and/or determining the activity and/or efficacy of the bone disorder therapeutic agent, using suitable means, for example, J774 murine macrophage viability assays, the rabbit osteoclast cultures, osteoblast bone marrow co-culture assays, etc.

One aspect of the present invention pertains to a bone disorder therapeutic agent identified by such methods.

Routes of Administration

The active compound or pharmaceutical composition comprising the active compound may be administered to a subject by any convenient route of administration, whether systemically/peripherally or topically (i.e., at the site of desired action).

Routes of administration include, but are not limited to, oral (e.g., by ingestion); buccal; sublingual; transdermal (including, e.g., by a patch, plaster, etc.); transmucosal (including, e.g., by a patch, plaster, etc.); intranasal (e.g., by nasal spray); ocular (e.g., by eyedrops); pulmonary (e.g., by inhalation or insufflation therapy using, e.g., via an aerosol, e.g., through the mouth or nose); rectal (e.g., by suppository or enema); vaginal (e.g., by pessary); parenteral, for example, by injection, including subcutaneous, intradermal, intramuscular, intravenous, intraarterial, intracardiac, intrathecal, intraspinal, intracapsular, subcapsular, intraorbital, intraperitoneal, intratracheal, subcuticular, intraarticular, subarachnoid, and intrasternal; by implant of a depot or reservoir, for example, subcutaneously or intramuscularly.

The Subject

The subject may be an animal, a chordate, a vertebrate, a mammal, a placental mammal, a marsupial (e.g., kangaroo, wombat), a monotreme (e.g., duckbilled platypus), a rodent (e.g., a guinea pig, a hamster, a rat, a mouse), murine (e.g., a mouse), a lagomorph (e.g., a rabbit), avian (e.g., a bird), canine (e.g., a dog), feline (e.g., a cat), equine (e.g., a horse), porcine (e.g., a pig), ovine (e.g., a sheep), bovine (e.g., a cow), a primate, simian (e.g., a monkey or ape), a monkey (e.g., marmoset, baboon), an ape (e.g., gorilla, chimpanzee, orangutang, gibbon), or a human.

Furthermore, the subject may be any of its forms of development, for example, a foetus.

In one preferred embodiment, the subject is a human.

Formulations

While it is possible for the active compound (e.g., cannabinoid receptor inverse agonist or cannabinoid receptor neutral antagonist, as described herein) to be administered alone, it is preferable to present it as a pharmaceutical formulation (e.g., composition, preparation, medicament) comprising at least one active compound, as defined above, together with one or more other pharmaceutically acceptable ingredients well known to those skilled in the art, including, but not limited to, pharmaceutically acceptable carriers, diluents, excipients, adjuvants, fillers, buffers, preservatives, anti-oxidants, lubricants, stabilisers, solubilisers, surfactants (e.g., wetting agents), masking agents, colouring agents, flavouring agents, and sweetening agents. The formulation may further comprise other active agents, for example, other therapeutic or prophylactic agents.

Thus, the present invention further provides pharmaceutical compositions, as defined above, and methods of making a pharmaceutical composition comprising admixing at least one active compound, as defined above, together with one or more other pharmaceutically acceptable ingredients well known to those skilled in the art, e.g., carriers, diluents, excipients, etc. If formulated as discrete units (e.g., tablets, etc.), each unit contains a predetermined amount (dosage) of the active compound.

The term "pharmaceutically acceptable" as used herein pertains to compounds, ingredients, materials, compositions, dosage forms, etc., which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of the subject in question (e.g., human) without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. Each carrier,

diluent, excipient, etc. must also be "acceptable" in the sense of being compatible with the other ingredients of the formulation.

Suitable carriers, diluents, excipients, etc. can be found in standard pharmaceutical texts, for example, Remington's Pharmaceutical Sciences, 18th edition, Mack Publishing Company, Easton, Pa., 1990; and Handbook of Pharmaceutical Excipients, 2nd edition, 1994.

The formulations may be prepared by any methods well known in the art of pharmacy. Such methods include the step of bringing into association the active compound with a carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active compound with carriers (e.g., liquid carriers, finely divided solid carrier, etc.), and then shaping the product, if necessary.

The formulation may be prepared to provide for rapid or slow release; immediate, delayed, timed, or sustained release; or a combination thereof.

Formulations may suitably be in the form of liquids, solutions (e.g., aqueous, non-aqueous), suspensions (e.g., aqueous, non-aqueous), emulsions (e.g., oil-in-water, water-in-oil), elixirs, syrups, electuaries, mouthwashes, drops, tablets (including, e.g., coated tablets), granules, powders, losenges, pastilles, capsules (including, e.g., hard and soft gelatin capsules), cachets, pills, ampoules, boluses, suppositories, pessaries, tinctures, gels, pastes, ointments, creams, lotions, oils, foams, sprays, mists, or aerosols.

Formulations may suitably be provided as a patch, adhesive plaster, bandage, dressing, or the like which is impregnated with one or more active compounds and optionally one or more other pharmaceutically acceptable ingredients, including, for example, penetration, permeation, and absorption enhancers. Formulations may also suitably be provided in the form of a depot or reservoir.

The active compound may be dissolved in, suspended in, or admixed with one or more other pharmaceutically acceptable ingredients. The active compound may be presented in a liposome or other microparticulate which is designed to target the active compound, for example, to blood components or one or more organs.

Formulations suitable for oral administration (e.g, by ingestion) include liquids, solutions (e.g., aqueous, non-aqueous), suspensions (e.g., aqueous, non-aqueous), emulsions

(e.g., oil-in-water, water-in-oil), elixirs, syrups, electuaries, tablets, granules, powders, capsules, cachets, pills, ampoules, boluses.

Formulations suitable for buccal administration include mouthwashes, losenges, pastilles, as well as patches, adhesive plasters, depots, and reservoirs. Losenges typically comprise the active compound in a flavored basis, usually sucrose and acacia or tragacanth. Pastilles typically comprise the active compound in an inert matrix, such as gelatin and glycerin, or sucrose and acacia. Mouthwashes typically comprise the active compound in a suitable liquid carrier.

Formulations suitable for sublingual administration include tablets, losenges, pastilles, capsules, and pills.

Formulations suitable for oral transmucosal administration include liquids, solutions (e.g., aqueous, non-aqueous), suspensions (e.g., aqueous, non-aqueous), emulsions (e.g., oil-in-water, water-in-oil), mouthwashes, losenges, pastilles, as well as patches, adhesive plasters, depots, and reservoirs.

Formulations suitable for non-oral transmucosal administration include liquids, solutions (e.g., aqueous, non-aqueous), suspensions (e.g., aqueous, non-aqueous), emulsions (e.g., oil-in-water, water-in-oil), suppositories, pessaries, gels, pastes, ointments, creams, lotions, oils, as well as patches, adhesive plasters, depots, and reservoirs.

Formulations suitable for transdermal administration include gels, pastes, ointments, creams, lotions, and oils, as well as patches, adhesive plasters, bandages, dressings, depots, and reservoirs.

Tablets may be made by conventional means, e.g., compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active compound in a free-flowing form such as a powder or granules, optionally mixed with one or more binders (e.g., povidone, gelatin, acacia, sorbitol, tragacanth, hydroxypropylmethyl cellulose); fillers or diluents (e.g., lactose, microcrystalline cellulose, calcium hydrogen phosphate); lubricants (e.g., magnesium stearate, talc, silica); disintegrants (*e.g.*, sodium starch glycolate, cross-linked povidone, cross-linked sodium carboxymethyl cellulose); surface-active or dispersing or wetting agents (e.g., sodium lauryl sulfate); preservatives (e.g., methyl p-hydroxybenzoate, propyl p-hydroxybenzoate, sorbic acid); flavours, flavour enhancing agents, and sweeteners. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets

may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active compound therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile. Tablets may optionally be provided with a coating, for example, to affect release, for example an enteric coating, to provide release in parts of the gut other than the stomach.

Ointments are typically prepared from the active compound and a paraffinic or a water-miscible ointment base.

Creams are typically prepared from the active compound and an oil-in-water cream base. If desired, the aqueous phase of the cream base may include, for example, at least about 30% w/w of a polyhydric alcohol, i.e., an alcohol having two or more hydroxyl groups such as propylene glycol, butane-1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol and mixtures thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the active compound through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethylsulfoxide and related analogues.

Emulsions are typically prepared from the active compound and an oily phase, which may optionally comprise merely an emulsifier (otherwise known as an emulgent), or it may comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabiliser. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabiliser(s) make up the so-called emulsifying wax, and the wax together with the oil and/or fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

Suitable emulgents and emulsion stabilisers include Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol, glyceryl monostearate and sodium lauryl sulphate. The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of the active compound in most oils likely to be used in pharmaceutical emulsion formulations may be very low. Thus the cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in

combination depending on the properties required. Alternatively, high melting point lipids such as white-soft-paraffin-and/or-liquid paraffin-or-other mineral oils can be used.

Formulations suitable for intranasal administration, where the carrier is a liquid, include, for example, nasal spray, nasal drops, or by aerosol administration by nebuliser, include aqueous or oily solutions of the active compound.

Formulations suitable for intranasal administration, where the carrier is a solid, include, for example, those presented as a coarse powder having a particle size, for example, in the range of about 20 to about 500 microns which is administered in the manner in which snuff is taken, i.e., by rapid inhalation through the nasal passage from a container of the powder held close up to the nose.

Formulations suitable for pulmonary administration (e.g., by inhalation or insufflation therapy) include those presented as an aerosol spray from a pressurised pack, with the use of a suitable propellant, such as dichlorodifluoromethane, trichlorofluoromethane, dichoro-tetrafluoroethane, carbon dioxide, or other suitable gases.

Formulations suitable for ocular administration include eye drops wherein the active compound is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active compound.

Formulations suitable for rectal administration may be presented as a suppository with a suitable base comprising, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols, for example, cocoa butter or a salicylate; or as a solution or suspension for treatment by enema.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active compound, such carriers as are known in the art to be appropriate.

Formulations suitable for parenteral administration (e.g., by injection), include aqueous or non-aqueous, isotonic, pyrogen-free, sterile liquids (e.g., solutions, suspensions), in which the active compound is dissolved, suspended, or otherwise provided (e.g., in a liposome or other microparticulate). Such liquids may additional contain other pharmaceutically acceptable ingredients, such as anti-oxidants, buffers, preservatives, stabilisers, bacteriostats, suspending agents, thickening agents, and solutes which render the formulation isotonic with the blood (or other relevant bodily fluid) of the intended recipient. Examples of excipients include, for example, water, alcohols, polyols, glycerol, vegetable

oils, and the like. Examples of suitable isotonic carriers for use in such formulations include Sodium Chloride Injection, Ringer's Solution, or Lactated Ringer's Injection. Typically, the concentration of the active compound in the liquid is from about 1 ng/mL to about 10 µg/mL, for example from about 10 ng/ml to about 1 µg/mL. The formulations may be presented in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules, and tablets.

Dosage

It will be appreciated by one of skill in the art that appropriate dosages of the cannabinoid receptor inverse agonists or cannabinoid receptor neutral antagonists, and compositions comprising them, can vary from patient to patient. Determining the optimal dosage will generally involve the balancing of the level of therapeutic benefit against any risk or deleterious side effects. The selected dosage level will depend on a variety of factors including, but not limited to, the activity of the particular compound, the route of administration, the time of administration, the rate of excretion of the compound, the duration of the treatment, other drugs, compounds, and/or materials used in combination, the severity of the condition, and the species, sex, age, weight, condition, general health, and prior medical history of the patient. The amount of compound and route of administration will ultimately be at the discretion of the physician, veterinarian, or clinician, although generally the dosage will be selected to achieve local concentrations at the site of action which achieve the desired effect without causing substantial harmful or deleterious side-effects.

Administration can be effected in one dose, continuously or intermittently (e.g., in divided doses at appropriate intervals) throughout the course of treatment. Methods of determining the most effective means and dosage of administration are well known to those of skill in the art and will vary with the formulation used for therapy, the purpose of the therapy, the target cell(s) being treated, and the subject being treated. Single or multiple administrations can be carried out with the dose level and pattern being selected by the treating physician, veterinarian, or clinician.

In general, a suitable dose of the active compound is in the range of about 100 µg to about 250 mg (more typically about 100 µg to about 25 mg) per kilogram body weight of the subject per day. Where the active compound is a salt, an ester, an amide, a prodrug,

or the like, the amount administered is calculated on the basis of the parent compound and so the actual weight to be used is increased proportionately.

Kits

One aspect of the invention pertains to a kit comprising (a) an active compound (e.g., cannabinoid receptor inverse agonist or cannabinoid receptor neutral antagonist), as described herein, or a composition comprising an active compound, as described herein, e.g., preferably provided in a suitable container and/or with suitable packaging; and (b) instructions for use, e.g., written instructions on how to administer the compound or composition.

The written instructions may also include a list of indications for which the active ingredient is a suitable treatment.

Mechanism of Action

The inventors have shown that inverse agonists (as discussed above, inverse agonists can both block the action of the agonist and attenuate receptor constitutive activity) of the cannabinoid receptors CB1 and CB2 have potent inhibitory effects on survival of J774 macrophages (an established model system to test for compounds which inhibit osteoclastic activity; see, e.g., Rogers et al., 1996) and on the survival and resorptive activity of isolated rabbit osteoclasts. This identifies the endocannabinoid system as a novel therapeutic target for the treatment of bone diseases. The data are consistent with a model whereby the survival and activity of osteoclasts is regulated by CB receptor activation.

More particularly, the inventors have found that inverse agonists of the CB1/CB2 receptors (AM251, AM630, SR144528, and JTE-907) modulated J774 survival in a concentration dependent manner. In addition, AM251 and SR144528 were found to inhibit survival and resorptive activity of authentic rabbit osteoclasts and to completely reverse ovariectomy-induced bone loss in a mouse model. These data suggest that CB receptors are the molecular target and that inverse agonists of CB receptors have inhibitory effects on bone resorption.

The data presented herein indicate that the CB inverse agonists AM251, AM630, SR144528, and JTE-907 have potent inhibitory effects on J774 survival and rabbit osteoclast survival and resorptive activity. It is known that CB2 receptor expression predominates in cells of macrophage lineage. These data therefore suggest that

inhibition of osteoclast survival by AM251, AM630, SR144528, and JTE-907 may be CB2 receptor mediated. However, inverse agonism at the CB1 receptor or synergistic effect of CB1 and CB2 receptors in osteoclasts cannot be ruled out. These compounds are known to be inverse agonists at CB1 and CB2 receptors. In terms of affinity, AM251 is CB1 selective and AM630, SR144528 and JTE-907 are CB2 selective; however, the relative potency of these compounds as inverse agonists at each subtype is not known. Thus, although AM251 is CB1 selective, it also has affinity for the CB2 receptor and may also be a potent CB2 receptor inverse agonist.

It is important to point out that tone in the endocannabinoid system may exist either via constitutively active CB receptors or via an ongoing release of endogenous CB receptor agonists. It is known that J774 macrophages synthesise and release endocannabinoids and contain the enzymes responsible for the endocannabinoid inactivation (see, e.g., Di et al., 1996). In view of this, it is possible that autocrine release of endocannabinoids plays a role in J774 survival and that inhibition of receptor binding by AM251 or related compounds will compromise J774 survival (and by implication, osteoclast survival) by disrupting this autocrine loop.

Whilst the data presented herein suggest that the CB2 receptor is the target site of interest, it is important to note that the pharmacology of anandamide and other endocannabinoids is highly complex. Thus, the pharmacological characteristics of these eicosanoids indicate that their actions may be mediated by cannabinoid CB1 and CB2 receptors and by putative non-CB1, non-CB2 or "CB2-like" receptors (see, e.g., Pertwee et al., 2002; Di et al., 1998; Di et al., 2002).

Anandamide also interacts with vanilloid TRPV1 receptors both directly (see, e.g., Zygmunt et al., 1999; Ross et al., 2001) and indirectly via metabolites (see, e.g., Craib et al., 2001). Anandamide is subject to rapid intracellular hydrolysis by fatty acid amide hydrolase (FAAH) to yield arachidonic acid and ethanolamide. Recent work suggests that anandamide may also be metabolised by a range of oxygenase enzymes already known to convert arachidonic acid to a number of potent biologically active compounds (see, e.g., Kozak et al., 2002). In addition, SR141716A, which is structurally related to AM251, interacts with both TRPVR1 receptors and non-CB1 receptors (see, e.g., Pertwee et al., 2002). Consequently, it is possible that cannabinoid-related compounds such AM251, AM630, SR144528, and JTE-907 may be acting at a novel target site of action, which may be a receptor, ion-channel or metabolic enzyme. Alternatively, the compounds may be achieving inhibition via an interaction with both CB1 and CB2 receptors: AM251 and AM630 both interact with both the CB1 and the CB2 receptor. There is evidence that of

synergism between CB1 and CB2 receptor in effecting the anti-inflammatory action of endocannabinoids (see, e.g., Calignano et al., 1998).

The following Table summarises the results obtained in the J774 viability assay. The data demonstrate that:

(a) the inverse agonists AM251 and AM630, which are from different chemical classes, inhibit J774 viability;

(b) the endocannabinoid anandamide, which is an antagonist at the CB2 receptor, also inhibits J774 viability;

(c) the non-selective CB1/CB2 receptor agonists WIN55212 and CP55940 do not affect J774 viability;

(d) the CB2 selective agonist JWH-133 also does not affect viability.

The data therefore suggest that cannabinoid receptor inverse agonist/antagonists are effective in the J774 viability assay.

Table 2

Compound	Chemical Class	CB receptor function	IC_{50} in J774 cells
Anandamide	Endocannabinoid	CB1 agonist CB2 partial agonist/antagonist	40 μM
AM251	Pyrazole	CB1 inverse agonist	5 μM
AM630	Indole	CB1 inverse agonist CB2 inverse agonist	20 μM
WIN55212	Indole	CB1 agonist CB2 agonist	inactive
JWH 133	Classical Cannabinoid	CB2-selective agonist	inactive
CP55940	Classical Cannabinoid	CB1 agonist CB2 agonist	inactive
SR144528	Pyrazole	CB2 inverse agonist	9 uM
JTE-907	2-Oxoquinoline	CB2 inverse agonist	25 uM

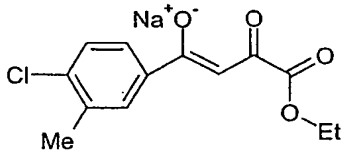
EXAMPLES

The following examples are provided solely to illustrate the present invention and are not intended to limit the scope of the invention, as described herein.

Synthesis Examples

Synthesis Example 1-1

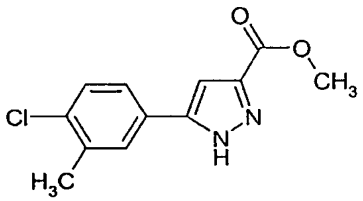
Sodium salt of 4-(4-chloro-3-methyl-phenyl)-4-oxido-2-oxo-but-3-enoic acid ethyl ester



Sodium (1.36 g) was dissolved in methanol (35 ml) and cooled to room temperature. 4-Chloro-3-methylacetophenone (10 g) was added followed by diethyl oxalate (8 ml) in methanol (10 ml). A slurry resulted. Addition of methanol (10 ml) failed to fluidise the mixture and it was left to stand for 2 hrs. Diethyl ether (150 ml) was added and the suspension stirred for 1 hr. Filtration and washing with ether gave the title product as a pale green solid.

Synthesis Example 1-2

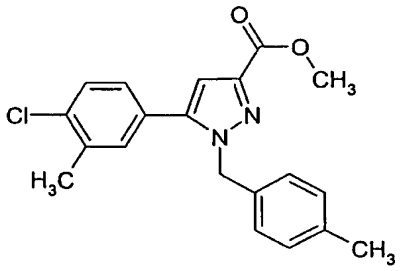
5-(4-Chloro-3-methyl-phenyl)-1H-pyrazole-3-carboxylic acid methyl ester



The 4-(4-chloro-3-methyl-phenyl)-4-oxido-2-oxo-but-3-enoic acid ethyl ester (8.8 g) was dissolved in acetic acid (100 ml) with gentle heating. After cooling to room temperature, hydrazine monohydrate (1.7 ml) was added dropwise. The solution was refluxed for 4.5 hours and then stirred overnight, after which a solid had been precipitated. The solid was filtered and washed with water. Recrystallisation from ethanol gave the title product as a white solid.

Synthesis Example 1-3

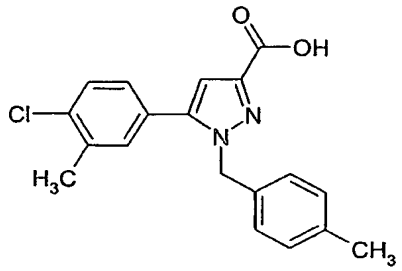
5-(4-Chloro-3-methyl-phenyl)-1-(4-methyl-benzyl)-1H-pyrazole-3-carboxylic acid methyl ester



5-(4-Chloro-3-methyl-phenyl)-1H-pyrazole-3-carboxylic acid methyl ester (2.5 g) was suspended in toluene (25 ml) and added dropwise to a suspension of 60% NaH (0.95 g) in toluene (25 ml). The mixture was stirred at 65°C for 1 hour. 4-Methylbenzyl bromide (2 g) was added and the suspension refluxed overnight. After cooling, the reaction was quenched with saturated NH_4Cl (50 ml). The organic phase was separated and washed with saturated NaCl, dried over $MgSO_4$ and evaporated to give a clear oil which solidified on standing. Purified by column chromatography (toluene : DCM : ethyl acetate, 8:1:1). δ_C ($CDCl_3$, 62.9 MHz): 20.0, 21.1, 52.1, 54.1, 109.5, 126.9, 127.6, 128.0, 129.4, 131.6, 133.5, 135.5, 136.7, 137.6, 142.8, 144.4 and 162.9. δ_H ($CDCl_3$, 250 MHz): 2.30 (3H, s), 2.33 (3H, s), 3.94 (3H, s), 5.33 (2H, s) and 6.84-7.35 (8H, m).

Synthesis Example 1-4

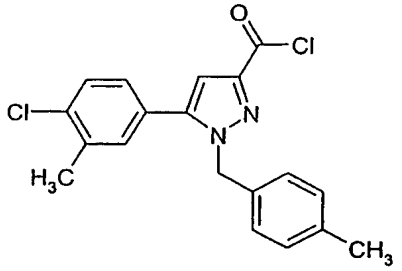
5-(4-Chloro-3-methyl-phenyl)-1-(4-methyl-benzyl)-1H-pyrazole-3-carboxylic acid



5-(4-Chloro-3-methyl-phenyl)-1-(4-methyl-benzyl)-1H-pyrazole-3-carboxylic acid methyl ester (1.2 g) was dissolved in ethanol (50 ml). A solution of KOH (0.35 g) in water (10 ml) was added and the solution refluxed overnight. The solvent was evaporated and the white residue dissolved in water (100 ml), washed with ether, acidified to pH 2 with conc. HCl. Filtration gave the title product as a white solid (0.8 g). δ_C ($CDCl_3$, 62.9 MHz): 20.1, 21.1, 54.2, 109.9, 127.0, 127.7, 127.9, 128.9, 129.4, 131.6, 133.3, 135.6, 136.7, 137.8, 142.3, 144.8 and 166.4.

Synthesis Example 1-5

5-(4-Chloro-3-methyl-phenyl)-1-(4-methyl-benzyl)-1H-pyrazole-3-carbonyl chloride

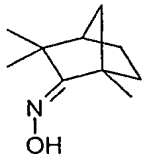


5-(4-Chloro-3-methyl-phenyl)-1-(4-methyl-benzyl)-1H-pyrazole-3-carboxylic acid (0.8 g) was placed in toluene (30 ml). Thionyl chloride (2 ml) was added and the mixture refluxed

for 4 hours. The solvent was evaporated to give a yellow oil. The oil was dissolved in 30 ml-toluene-and-again refluxed-with-thionyl-chloride for 2 hours. Evaporation of the solvent gave the title product.

Synthesis Example 1-6

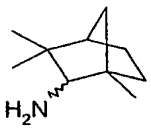
(1S)-1,3,3-Trimethyl-bicyclo[2.2.1]heptan-2-one oxime



Hydroxylamine hydrochloride (11.5 g) and sodium acetate (20.5 g) were dissolved in water (100 ml), added to a solution of fenchone (19 g) in methanol (60 ml) and refluxed for 48 hours. After cooling, the large white needles were filtered, washed with water and dried under vacuum to give the title product (20 g).

Synthesis Example 1-7

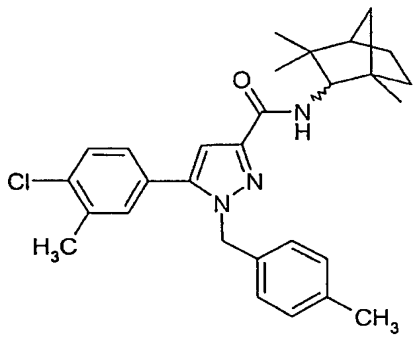
(1S)-1,3,3-trimethylbicyclo[2.2.1]hept-2-endo,exo-yl-amine



(1S)-1,3,3-Trimethyl-bicyclo[2.2.1]heptan-2-one oxime (5 g) was dissolved in acetic acid (35 ml) and chilled in an ice bath. Activated Raney Nickel (15 g) was added, the mixture warmed to room temperature and stirred overnight under an atmosphere of hydrogen. The catalyst was filtered off using celite and washed through with a further portion of acetic acid (20 ml). Ice water (200 ml) was added to the filtrate and the pH adjusted to 7 using conc. NaOH solution. A green emulsion was produced. The emulsion was extracted with ether. The ether layer was dried and evaporated to give a white sludge. Addition of ether gave a white solid. Filtration gave the title product as a 1:1 mixture of the two isomers (1.2 g). δ_C ($CDCl_3$, 62.9 MHz): 17.4, 19.4, 20.5, 23.2, 23.7, 25.3, 25.8, 26.0, 26.5, 30.9, 35.8, 38.7, 41.2, 42.5, 42.7, 48.0, 48.4, 48.9, 66.1 and 67.0.

Synthesis Example 1-8

5-(4-Chloro-3-methyl-phenyl)-1-(4-methyl-benzyl)-1H-pyrazole-3-carboxylic acid ((1S)-1,3,3-trimethylbicyclo[2.2.1]hept-2-endo,exo-yl)-amide



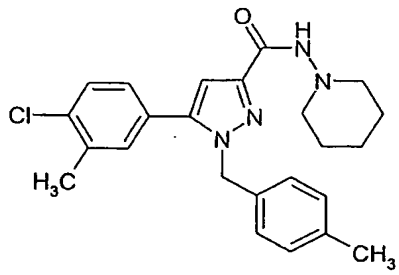
(1S)-1,3,3-trimethylbicyclo[2.2.1]hept-2-endo,exo-yl-amine (0.6 g) was suspended in DCM (20 ml) and 2 ml triethylamine. 5-(4-Chloro-3-methyl-phenyl)-1-(4-methyl-benzyl)-1H-pyrazole-3-carbonyl chloride (0.8 g) was dissolved in DCM (30 ml), added dropwise to the amine suspension and left to stir overnight at room temperature. The solvent was evaporated and the residue extracted with ethyl acetate. The organic phase was filtered and washed with saturated $NaHCO_3$ and NaCl solutions, dried over Na_2SO_4, and evaporated to give an oil. The product was purified by column chromatography using petrol:ethyl acetate (9:1). Four spots were seen by thin layer chromatography (TLC), the central pair being the desired product endo/exo isomers. Repeated column chromatography gave the exo-isomer (first fraction) (220 mg) and the endo-isomer (180 mg) as amorphous solids.

Exo isomer: δ_C ($CDCl_3$, 62.9 MHz): 19.8, 20.1, 21.1, 21.3, 26.1, 27.4, 31.0, 39.5, 42.7, 48.2, 48.7, 53.6, 63.0, 107.1, 126.7, 127.5, 128.5, 129.4, 131.5, 133.9, 135.3, 136.6, 137.3, 144.7, 146.3 and 162.6. δ_H ($CDCl_3$, 250 MHz): 0.87 (3H, s), 1.11 (3H, s), 1.17 (3H, s), 1.23 - 1.77 (7H, m), 2.32 (6H, s), 3.80 (1H, d, J 9.8), 5.27 (2H, s), 5.29 (1H, m), 6.82 (1H, s), 6.93 (2H, d, *J* 7.94), 7.02 (2H, d, *J* 7.94), 7.09 (2H, m) and 7.33 (1H, d, *J* 8.24).

Endo isomer: δ_C ($CDCl_3$, 62.9 MHz): 17.9, 20.1, 21.1, 24.6, 25.6, 26.9, 35.5, 42.3, 43.5, 48.3, 48.4, 53.6, 64.4, 107.1, 126.7, 127.5, 128.5, 129.4, 131.5, 133.9, 135.3, 136.6, 137.3, 144.7, 146.3 and 162.6. δ_H ($CDCl_3$, 250 MHz): 0.95 (3H, s), 1.08 (3H, s), 1.15 (3H, s), 1.20 – 1.71 (7H, m), 2.32 (6H, s), 3.60 (1H, d, J 10.4), 5.27 (2H, s), 6.83 (1H, s), 6.93 (2H, d, *J* 7.94), 7.02 (2H, d, *J* 7.94), 7.09 (2H, m) 7.24 (1H, m) and 7.33 (1H, d, *J* 8.24).

Synthesis Example 2

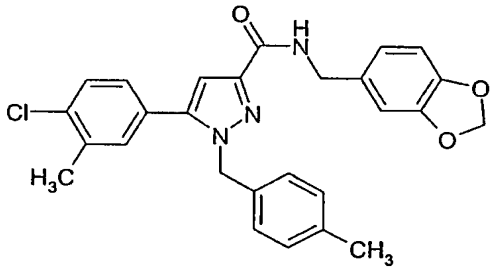
5-(4-Chloro-3-methyl-phenyl)-1-(4-methyl-benzyl)-1H-pyrazole-3-carboxylic acid piperidin-1-yl amide



N-Aminopiperidine (0.5 g) was suspended in DCM (20 ml) and 1 ml triethylamine. 5-(4-Chloro-3-methyl-phenyl)-1-(4-methyl-benzyl)-1H-pyrazole-3-carbonyl chloride (0.4 g) (see above) was dissolved in DCM (5 ml), added dropwise to the suspension, and left to stir overnight at room temperature. The solvent was evaporated and the residue extracted with ethyl acetate. The organic phase was filtered and washed with saturated $NaHCO_3$ and NaCl solutions, dried over Na_2SO_4, and evaporated to give the title compound as an oil. The product was purified by column chromatography using petrol : ethyl acetate (1:1) to give a white solid (65%). δ_C ($CDCl_3$, 62.9 MHz): 20.1, 21.1, 23.3, 25.3, 53.5, 57.2, 107.7, 126.6, 127.4, 128.3, 129.5, 131.2, 131.5, 133.7, 135.4, 136.7, 137.6, 144.7, 145.6 and 159.2. δ_H ($CDCl_3$, 250 MHz): 1.43 (2H, m), 1.75 (4H, m), 2.32 (6H, s), 2.88 (4H, m), 5.25 (2H, s), 6.88 (1H, s), 6.91 (2H, d, J 8.24), 7.02 (2H, d, J 8.24), 7.09 (2H, d, J 7.02), 7.25 (1H, m), 7.33 (1H, d, J 8.24) and 7.66 (1H, br s).

Synthesis Example 3

5-(4-Chloro-3-methyl-phenyl)-1-(4-methyl-benzyl)-1H-pyrazole-3-carboxylic acid (benzo[1,3]dioxol-5-yl-methyl) amide



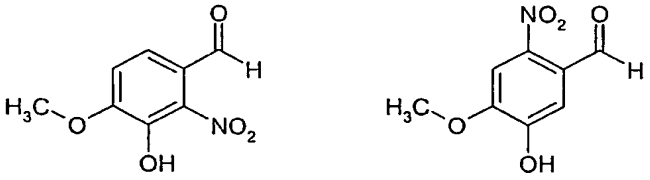
3,4-Methylenedioxybenzylamine (0.5 g) was suspended in DCM (20 ml) and 1 ml triethylamine. 5-(4-Chloro-3-methyl-phenyl)-1-(4-methyl-benzyl)-1H-pyrazole-3-carbonyl chloride (0.4 g) (see above) was dissolved in DCM (5 ml), added dropwise to the suspension and left to stir overnight at room temperature. The solvent was evaporated and the residue extracted with ethyl acetate. The organic phase was filtered and washed with saturated $NaHCO_3$ and NaCl solutions, dried over Na_2SO_4 and evaporated to give the

title compound as an oil. The product was purified by column chromatography using petrol : ethyl acetate (9:1). δ_C ($CDCl_3$, 62.9 MHz): 20.1, 21.1, 43.0, 53.5, 101.0, 107.3, 108.3, 108.6, 121.2, 126.6, 127.5, 128.3, 129.5, 131.2, 131.5, 132.4, 133.7, 135.4, 136.7, 137.7, 144.9, 146.0, 146.9, 147.9 and 161.8. δ_H ($CDCl_3$, 250 MHz): 2.31 (3H, s), 2.34 (3H, s), 4.52 (2H, d, J 5.8), 5.23 (2H, s), 5.92 (2H, s), 6.76 – 7.12 (9 H, m) 7.21 (1H, m), and 7.34 (1H, d, J 8.24).

Synthesis Example 4-1

3-Hydroxy-4-methoxy-2-nitro-benzaldehyde

3-Hydroxy-4-methoxy-6-nitro-benzaldehyde

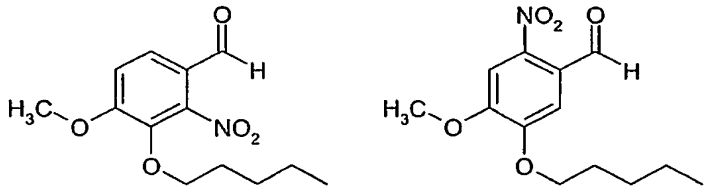


3-Hydroxy-4-methoxy-benzaldehyde (15.2 g) was dissolved in THF (150 ml). $NaNO_3$ (8.5 g) and lanthanum nitrate hexahydrate (8.7 g) were added. A mixture of conc. HCl (35 ml) and water (35 ml) was added dropwise over 20 minutes and the reaction mixture stirred at room temperature for 1 hour. The mixture was extracted with ethyl acetate and diethyl ether. Each of the organic phases was washed with water (50 ml) saturated Na_2CO_3 (50 ml) and saturated NaCl (50 ml). Drying and evaporation gave the title compounds as a crude mixture.

Synthesis Example 4-2

4-Methoxy-2-nitro-3-pentyloxy-benzyaldehyde

4-Methoxy-6-nitro-3-pentyloxy-benzyaldehyde



3-Hydroxy-4-methoxy-2-nitro-benzaldehyde (as a crude mixture of products from the previous example) (12.3 g) was dissolved in DMF (20 ml). Bromopentane (11.3 g) and anhydrous K_2CO_3 (12.9 g) were added. The suspension was stirred in a boiling water bath for 5 hours. The mixture was cooled, filtered and saturated NH_4Cl (200 ml) added to the filtrate. The filtrate was extracted with ethyl acetate and this was washed with saturated NaCl and dried. Evaporation and purification with column chromatography (petrol:ethyl acetate, 5:1) gave the title compounds as a crude mixture.

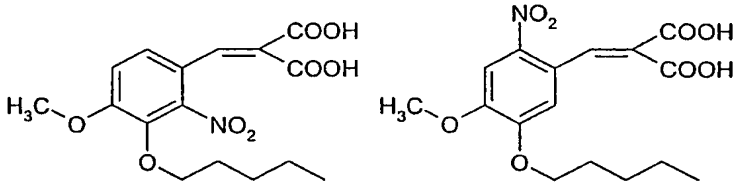
A crude sample of 4-Methoxy-2-nitro-3-pentyloxy-benzyaldehyde was obtained, contaminated with starting materials.—

A pure sample of 4-Methoxy-6-nitro-3-pentyloxy-benzyaldehyde was obtained as yellow crystals by column chromatography (petrol:ethyl acetate, 6:1) or by repeated crystallisation with petrol / diethyl ether. δ_C ($CDCl_3$, 62.9 MHz): 13.9, 22.4, 27.9, 28.5, 56.8, 69.9, 107.3, 110.5, 125.6, 143.6, 152.5, 153.0, and 187.8.

Synthesis Example 4-3

2-(4-Methoxy-2-nitro-3-pentyloxy-benzylidene) malonic acid

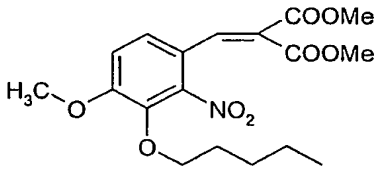
2-(4-Methoxy-6-nitro-3-pentyloxy-benzylidene) malonic acid



The mixture of products from the previous example (6 g) were dissolved in acetic acid (65 ml). Malonic acid (7 g) was added and the mixture stirred at 60°C for 24 hours. The solvent was evaporated with the addition of toluene (2 x 100 ml). Water was added to the residue followed by NaOH solution to adjust the pH to 8, which allowed the product to go into solution. The aqueous was washed with ethyl acetate and then re-acidified with conc. HCl. The aqueous was extracted with ethyl acetate and the organic phase washed with saturated NaCl, dried and evaporated to give a mixture of the title compounds as a red solid.

Synthesis Example 4-4

2-(4-Methoxy-2-nitro-3-pentyloxy-benzylidene) malonic acid methyl diester

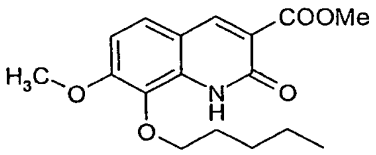


The crude mixture from the previous example (6 g) was dissolved in DMF (40 ml). Methyl iodide (4.4 ml) was added followed by K_2CO_3 (6.65 g) and the mixture was stirred at room temperature for 4 hrs. A saturated solution of NH_4Cl (200 ml) was added and the mixture extracted with ethyl acetate. The organic was washed with water, saturated NaCl and dried (Na_2SO_4). Evaporation gave a brown solid. Repeated crystallisations from ether / petrol gave 2-(4-methoxy-6-nitro-3-pentyloxy-benzylidene) malonic acid methyl diester as yellow needles δ_C (DMSO, 62.9 MHz): 14.0, 22.4, 27.9, 28.5, 52.6, 52.8, 56.5, 69.8,

108.0, 112.0, 124.4, 127.5, 139.7 142.2, 149.8, 153.0, 163.9 and 166.0 and the title compound as a crude red oil.

Synthesis Example 4-5

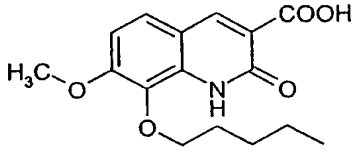
7-Methoxy-2-oxo-8-pentyloxy-1,2-dihydro-quinoline-3-carboxylic acid methyl ester



2-(4-Methoxy-2-nitro-3-pentyloxy-benzylidene) malonic acid methyl diester (5 g) was dissolved in acetic acid (60 ml) and water (4 ml) and stirred at 60°C. Reduced iron (6 g) was added and the mixture stirred at 90°C for 2 hours. The mixture was filtered and water (200 ml) was added. The solution was extracted with ethyl acetate and DCM. Each of the organic phases was washed with 1% HCl and saturated NaCl solutions. The organic phases were combined and evaporated. The product was dissolved in DCM and purified by column chromatography. The column was flushed with ethyl acetate : petrol, 1:1, and the product then eluted using ethanol. Evaporation gave the title compound as a white solid (1.6 g). δ_C ($CDCl_3$, 62.9 MHz): 14.0, 22.5, 27.9, 29.8, 52.5, 56.3, 73.8, 108.5, 113.3, 119.6, 125.2, 132.2, 134.5, 146.2, 154.8, 159.2 and 165.3. δ_H ($CDCl_3$, 250 MHz): 0.90 (3H, t, *J* 7.2), 1.38 (4H, m), 1.77 (2H, t, *J* 7.2), 3.91 (3H, s), 3.94 (3H, s), 4.08 (2H, t, *J* 6.9), 6.86 (1H, t, *J* 9.0), 7.33 (1H, d, t 9.0), 8.5 (1H, s) and 9.08 (1H, br s).

Synthesis Example 4-6

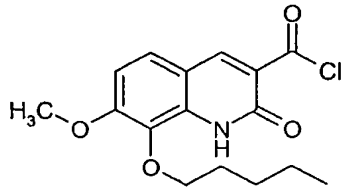
7-Methoxy-2-oxo-8-pentyloxy-1,2-dihydro-quinoline-3-carboxylic acid



7-Methoxy-2-oxo-8-pentyloxy-1,2-dihydro-quinoline-3-carboxylic acid methyl ester (440 mg) was dissolved in methanol (13 ml) with heating. A solution of NaOH (220 mg) in water (5.5 ml) was added and the mixture stirred at 50°C for 2 hours. The reaction was cooled in an ice bath and acidified with conc. HCl, giving a precipitate. The mixture was extracted with ethyl acetate and the organic phase dried over Na_2SO_4 and evaporated. Recrystallisation from ethanol gave the title compound as a white powder (300 mg). δ_C ($CDCl_3$, 62.9 MHz): 14.0, 22.4, 27.9, 29.8, 56.5, 74.0, 110.3, 114.4, 115.4, 126.0, 133.0, 133.6, 147.4, 155.5, 164.2 and 165.2. δ_H ($CDCl_3$, 250 MHz): 0.90 (3H, t, *J* 6.9), 1.39 (4H, m), 1.80 (2H, m), 4.0 (3H, s), 4.17 (2H, t, *J* 7.0), 7.02 (1H, d, *J* 8.9), 7.48 (1H, s, *J* 8.8), 8.84 (1H, s), 10.0 (1H, br s) and 14.0 (1H, br s).

Synthesis Example 4-7

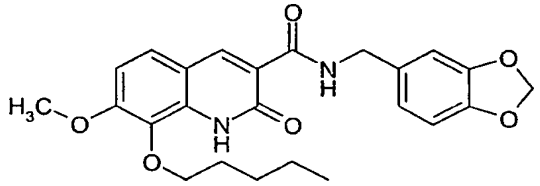
7-Methoxy-2-oxo-8-pentyloxy-1,2-dihydro-quinoline-3-carbonyl chorlide



7-Methoxy-2-oxo-8-pentyloxy-1,2-dihydro-quinoline-3-carboxylic acid (0.27 g) was dissolved in DCM (5 ml). A catalytic quantity of DMF was added followed by thionyl chloride (0.5 ml). The solution was stirred at room temperature for 1 hour. Toluene (2 x 10 ml) was added and the solvent evaporated. Upon cooling, the title compound was obtained as a yellow crystalline solid.

Synthesis Example 4-8

7-Methoxy-2-oxo-8-pentyloxy-1,2-dihydro-quinoline-3-carboxylic acid (benzo[1,3]dioxol-5-yl-methyl)-amide



3,4-methylenedioxybenzylamine (1 ml) was dissolved in DCM (10 ml). To this was added dropwise a solution of 7-methoxy-2-oxo-8-pentyloxy-1,2-dihydro-quinoline-3-carbonyl chloride in DCM (10 ml). A white precipitate is produced and the mixture stirred at room temperature for 2 hours. The solvent was evaporated, the residue dissolved in chloroform and purified by column chromatography ($CHCl_3$:ethyl acetate, 10:1). Evaporation gave a clear oil which solidified overnight to give the title compound as a white solid. δ_C ($CDCl_3$, 62.9 MHz): 14.0, 22.5, 28.0, 29.9, 43.3, 56.3, 73.8, 101.0, 108.3, 108.4, 109.1, 114.3, 119.5, 120.9, 125.4, 132.4, 132.6, 133.5, 145.1, 146.7, 147.8, 154.4, 162.1 and 163.6. δ_H ($CDCl_3$, 250 MHz): 0.91 (3H, t, J 7.1), 1.38 (4H, m), 1.78 (2H, m), 3.95 (3H, s), 4.11 (2H, t, J 6.8), 4.55 (2H, d, J 5.5), 5.90 (2H, s), 6.7-6.9 (3H, m), 6.92 (1H, d, J 8.8), 7.43 (1H, d, J 8.8), 8.86 (1H, s), 9.19 (1H, br s) and 9.93 (1H, br s).

Biological Methods

MTT J774 Murine Macrophage Viability Assay

Cultures of the murine macrophage cell line J774 is an established model system with which to screen for activity of agents that influence osteoclast function (see, e.g., Luckman et al., 1998).

MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) has an orange colour and is soluble in the medium used for cell culture. The mitochondrial enzyme succinate dehydrogenase acts upon MTT in living cells to produce the insoluble purple coloured formazan. The amount of formazan produced, as measured by UV/visible spectroscopy, is proportional to the number of viable cells.

J774 cells were plated at 10^4 cells per well in 150 µL αMEM in 96-well plates and grown overnight. The next day test compounds were added to the cultures, and cultures were continued for another 24-48 hours. At the end of the culture period, cell survival was determined using the tetrazolium dye-based MTT assay as previously described (see, e.g., MacPherson et al., 1999).

Briefly, MTT (5 mg/ml MTT in αMEM) was added to each well (1:10 v/v, 15 µL) and the cells incubated for 4 hours. The medium was carefully removed using a needle without dislodging the crystal layer. 100 µL acidified isopropanol (4 M HCl 1:100 v/v in isopropanol) was added to each well and the purple crystals allowed to dissolve. The absorbance was measured in a plate reader at 540 nm, with 690 nm as reference. The controls were a deep purple colour, indicating a high number of live cells. The results for each test compound were expressed as a % of the average control value.

In general, compounds studied were made up as 100 mM solutions in DMSO. These stock solutions were then diluted 100 x in culture medium. From these 1 mM solutions, convenient quantities (3-15 µL) were added directly to the wells so as to give the desired final compound concentration.

IC50 values for individual agents were calculated using GraphPad Prism (GraphPad Software, San Diego) and were defined as the concentration of agent required to reduce cell survival to 50% of the control value at 72 hours

Alamar Blue J774 Murine Macrophage Viability Assay

J774 cells were plated at 10^4 cells per well in 150 µL αMEM (α Modified Eagle Medium) in 96-well plates and grown overnight. The next day, compounds were added to the cultures, and culture was continued for another 72 hours. At the end of the culture period cell survival was determined using an Alamar Blue assay as previously described (see, e.g., Nociari et al., 1998).

Alamar Blue is an oxidation-reduction sensitive indicator. The dye itself is in the oxidised state, which is blue and non-fluorescent. The dye can accept electrons from reducing species, such as NADPH and FADH, to form a reduced dye species, which is red and fluorescent. Thus the transformation from oxidised form to reduced form can be measured by fluorimetric or colourimetric means. For fluorescence measurements, 530-560 nm excitation and 590 nm emission wavelengths are typically used. For colourimetric measurements, absorbance is measured at 570 nm (reduced form) and 600 nm (oxidised form) and a simple calculation performed to determine the relative quantities of the two species.

A high ratio of the reducing species, NADPH and FADH, to the corresponding oxidised species, NADP and FAD, is an indicator that cells are proliferating and viable. A low ratio indicates cells that are quiescent or non-viable.

Briefly, Alamar Blue (Biosource International) was added undiluted to the each well (1:10 v/v, 15 µL). The plate was incubated at 37°C for 3-4 hours and the fluorescence was measured at 570 nm, with a 25 nm bandwidth. A high reading indicated cells with normal viability, and a low reading indicates cells that have been damaged and are no longer proliferating normally. The controls gave a high fluorescence reading, indicating a high number of live, healthy cells. A potent test compound gave a low fluorescence reading. The average results for each test compound (e.g., n=5) were expressed as a % of the average control value.

In general, compounds studied were made up as 100 mM solutions in DMSO. These stock solutions were then diluted 100 or 1000 x in culture medium (αMEM). From these 1 mM or 100 µM solutions, convenient quantities (3-15 µL) were added directly to the wells so as to give the desired final compound concentration.

IC50 values for individual agents were calculated using GraphPad Prism (GraphPad Software, San Diego) and were defined as the concentration of agent required to reduce cell survival to 50% of the control value at 72 hours.

This assay offers numerous advantages over other assays, including MTT assays: it permits a higher throughput; it is more sensitive; it is non-damaging to the cells; it is faster; it generally gives an identical result to MTT assay.

Rabbit Osteoclast Culture

Osteoclast survival and activity was studied in cultures of rabbit osteoclasts. Osteoclasts were isolated from the long bones of 2-3 day-old rabbits as described previously (see, e.g., Coxon et al., 2000), plated on dentine slices and cultured in αMEM supplemented with 10% FCS and penicillin and streptomycin at 37°C in 5% CO_2 for 48 hours in the presence or absence of test compounds. At the end of the culture, the osteoclasts were identified by staining for tartrate-resistant acid phosphatase (TRAcP) and resorption pit area was quantified by reflected light microscopy as described previously (see, e.g., van't Hof et al., 1997).

Bone Marrow Co-Culture Assay

Osteoclast formation and activity was studied using an adaptation (see, e.g., van't Hof et al., 1997) of the osteoblast-bone marrow co-culture assay originally described previously (see, e.g., Takahashi et al., 1988). This is another experimental model system to screen for osteoclast-inhibitor and osteoclast-stimulatory agents.

Osteoblasts were isolated from the calvarial bones of 2-day-old mice by sequential collagenase digestion (type I collagenase, Sigma) and cultured in αMEM supplemented with 10% FCS and penicillin and streptomycin at 37°C in 5% CO_2. Bone marrow cell populations containing osteoclast precursors were isolated from the long bones of 3-5 month old mice and erythrocytes were removed by Ficoll Hypaque density gradient centrifugation. The resulting bone marrow cells were washed with PBS and resuspended in culture medium.

Osteoblasts and bone marrow cells were plated at 10^4 cells/well and $2x10^5$ cells/well, respectively, in 96-well plates in 150 µL of αMEM supplemented with 10% FCS, antibiotics and 10 nM 1,25-dihydroxyvitamin D_3. Test substances were added on day 7 and the cultures were terminated on day 10. At the end of the culture period, osteoclasts were identified by TRAcP staining and resorption pits were quantified by reflected light microscopy, as described above.

Mouse Osteoblast Culture

Osteoblasts were isolated as described above and plated at 10^4 cells/well in 96-well plates in 100 µL of αMEM supplemented with 10% FCS and antibiotics. Test substances were added after 24 hours and left for 72 hours. Cell viability was assessed using the Alamar Blue assay.

In Vivo Studies

Animals. Female 9 week-old C57/BL6 mice. Animals were housed in a designated animal facility and routinely maintained on a 12h:12h light:dark cycle and given ad libitum access to food and water.

Ovariectomy induced bone loss. Bilateral ovariectomy (Ovx) was performed under general anaesthesia. Sham ovariectomy (Sham) was similarly performed but with externalisation and replacement of the ovaries. Animals were given a daily injection of (a) candidate compound (e.g., 6 mg/kg) in vehicle (corn oil), or (b) vehicle (corn oil). After 21 days, the animals were killed, and the tibial bones were dissected and used for bone mineral density measurements and histomorphometric analysis (see below).

Bone Mineral Measurements. Measurements of bone mineral density (BMD) at the left proximal tibial metaphysis were determined by peripheral quantitative computed tomography (pQCT) using an XCT Research M bone densitometer with a voxel size of 70 µm and analysis software version 5.1.4. (Stratec Medizintechnik, Pforzheim, Germany). Daily quality assurance measurements were performed using a plexi-coated PVC-fluorinated hydrocarbon phantom according to the manufacturer's instructions.

Bone Histomorphometry. Histomorphometry was performed on left tibiae. The bones were dissected free of soft tissues, fixed in 4% buffered formalin/saline (pH 7.4) and embedded in methyl methacrylate. Longitudinal sections (4 µm) were then prepared and stained with Von Kossa and counterstained with Paragon. Histomorphometric measurements were made on sections of the proximal metaphysis distal to the epiphyseal growth plate at 20x magnification using a Zeiss Axioskop (Carl Zeiss, Welwyn Garden City, UK) coupled to an image analysis system running in-house designed software developed using Aphelion ActiveX Objects (Adcis SA, Hérouville-Saint-Clair, France). Bone histomorphometric variables were expressed according to the guidelines of the American Society of Bone and Mineral Research Nomenclature Committee (Eriksen, E.F., Axelrod, D.W., Melsen., F, 1994, Bone Histomorphometry, Raven Press, New York, USA).

Statistical Analyses. Statistical analyses were performed using SPSS for Windows version 9. Significant differences between groups were determined by ANOVA followed by post-hoc testing using Dunnet's post-test. All data are presented as means ± SEM unless stated otherwise. Values of p less than 0.05 were considered significant.

Dual Energy X-Ray Absorptiometry

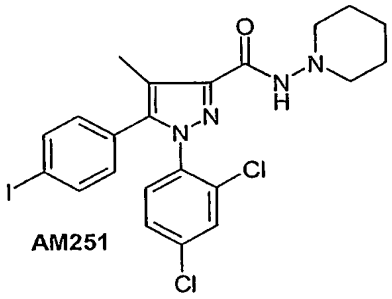
Whole body, spine and femoral bone mineral density (BMD) and bone mineral content (BMC) were determined using a Piximus small animal DEXA scanner at the start and the end of the experiment. Daily quality assurance measurements were performed using a phantom according to the manufacturer's instructions.

Biological Examples

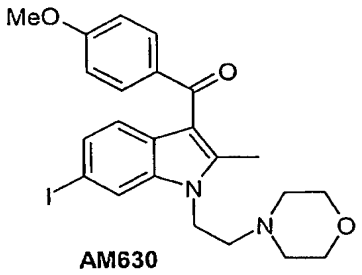
The following examples are provided solely to illustrate the present invention and are not intended to limit the scope of the invention, as described herein.

Biological Example 1

J774 murine macrophage viability studies were performed using the Alamar Blue assay, as described above, for the known cannabinoid receptors: CB1 inverse agonist AM251 and CB1/CB2 inverse agonist AM630.



AM251



AM630

Figure 1 is a graph showing J774 survival (% control) versus concentration of drug, for compounds AM630 (■) and AM251 (□) after 72 hours, by Alamar Blue assay (n=3).

The known CB1 receptor inverse agonist, AM251, was highly potent as a modulator of J774 survival after 72 hours (shown) and both 24 and 48 hours (data not shown), and had an IC50 of about 5 μM.

Similarly, the known CB2 receptor inverse agonist, AM630, also modulated J774 survival after 72 hours (shown) and both 24 and 48 hours (data not shown), with an IC50 of about 20 μM.

By comparison, the CB1/CB2 receptor agonists CP55940 and WIN 55212 did not affect J774 survival at concentrations of up to 100 μM (data not shown).

The known CB2 selective receptor agonist JWH133 did not affect J774 survival at concentrations of up to 20 μM (data not shown).

Also by comparison, the CB1 receptor agonist/CB2 receptor partial agonist anandamide (AEA) had no effect at low concentrations, but inhibited J774 survival at high concentrations with an IC50 of about 40 μM (data not shown).

This data demonstrates that CB receptor inverse agonists, such as AM251 and AM630 are highly active against macrophages and therefore have potential as potent osteoclast inhibitors.

Biological Example 2

The effects of the known cannabinoid receptor CB1 inverse agonist AM251 on isolated rabbit osteoclasts was studied using the rabbit osteoclast culture, as described above.

The results are shown in Figure 2 and Figure 3.

Figure 2 is a bar-graph of TRAcP MNC for control, AM251 (at 10 μM) ($p<0.03$), and AM251 (at 20 μM) ($p<0.01$).

Figure 3 is a bar-graph of resorbed area for control, AM251 (at 10 μM) ($p<0.03$), and AM251 (at 20 μM) ($p<0.01$).

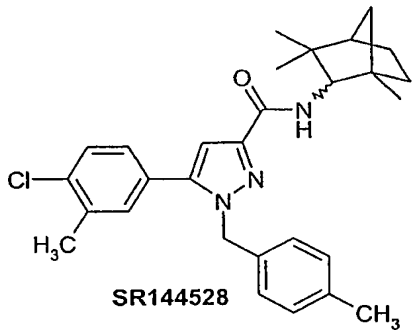
AM251 inhibited survival of tartrate resistant acid phosphatase positive multinucleated osteoclasts (TRAcP MNC).

AM251 also reduced bone resorption at concentrations of 10 μM and 20 μM.

This data demonstrates that the results obtained in the macrophage system are a viable model for osteoclast function and that the CB1 inverse agonist, AM251, is highly potent against rabbit osteoclast survival and function

Biological Example 3

The known cannabinoid receptor CB2 selective inverse agonist SR144528 and CB1 selective inverse agonist AM251, were studied in the osteoblast bone marrow co-culture assay, as described above.



SR144528

The osteoblast bone marrow co-culture assay data are shown in Figure 4 and Figure 5.

Figure 4 is a graph of TRAcP MNC versus concentration of AM251 (▣) and SR144528 ("SR144") (Δ) (n=3).

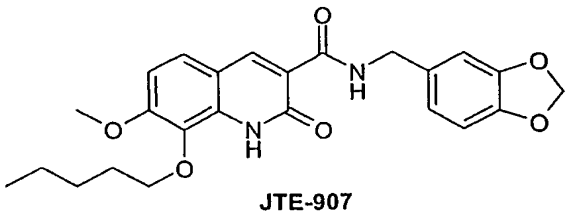
Figure 5 is a graph of resorbed area versus concentration of AM251 (■) and SR144528 ("SR144") (Δ) (n=3).

AM251 and SR144528 significantly inhibited osteoclast function, and significantly inhibited bone resorption, with an IC50 of about 5 μM.

These results demonstrate that both the CB2 selective inverse agonist SR144528 and the CB1 selective inverse agonist AM251 are highly potent against osteoclast survival and function.

Biological Example 4

The effects of known cannabinoid receptor ligands: CB2 inverse agonist SR144528; CB1 inverse agonist AM251; and CB2 inverse agonist JTE-907 were studied in the J774 murine macrophage system, assayed using Alamar Blue, as described above.



JTE-907

The Alamar Blue J774 murine macrophage viability assay data is shown in Figure 6.

Figure 6 is a graph of Alamar Blue J774 murine macrophage survival (% control) versus concentration of drug, for compounds AM251 (■), SR144528 ("SR144") (Δ) and JTE-907 ("JTE") (•) (n=3).

SR144528, JTE-907 and AM251 significantly inhibited J774 survival, with an IC50 of about 9 μM, about 25 μM, and about 7 μM, respectively.

These results demonstrate that both CB1 and CB2 receptor inverse agonists, such as SR144528, JTE-907 and AM251 are highly potent against macrophages. There does not appear to be a relationship between selectivity and activity.

Biological Example 5

The effects of the known cannabinoid receptor ligands: CB2 inverse agonist SR144528; CB1 inverse agonist AM251; and CB2 inverse agonist JTE-907, on isolated mouse osteoblasts was studied using the mouse osteoblast culture, as described above.

The mouse osteoblast culture data is shown in Figure 7

Figure 7 is a graph of osteoblast survival (% control) versus concentration of drug, for compounds SR144528 ("SR144") (Δ), AM251 (■) and JTE-907 ("JTE") (•) (n=3).

These results demonstrate that the CB1 selective inverse agonist AM251 is highly potent against osteoblasts whereas the CB2 selective inverse agonists SR144528 and JTE-907 show little activity. This suggests that CB2 selectivity may be important in the development of a suitable drug for treating bone loss.

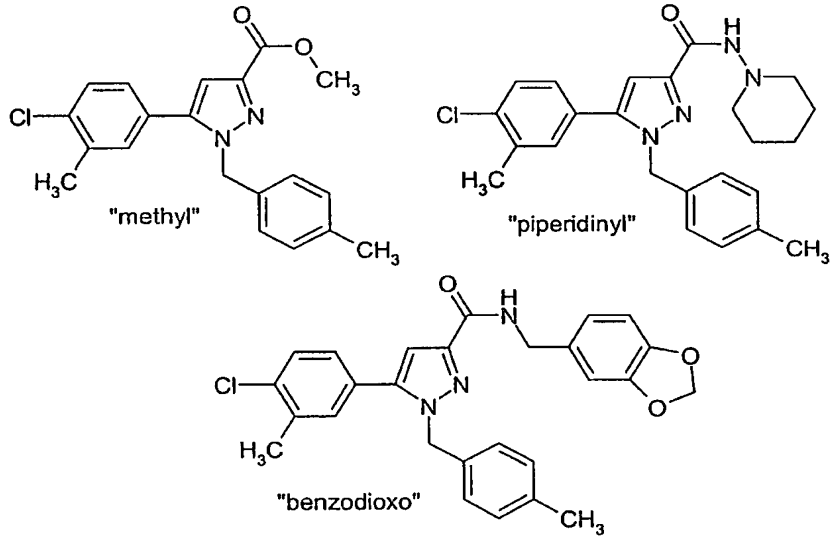
Biological Example 6

The effects of compounds related to SR144528 were further investigated using several SR144528 analogs of unknown biological function:

(a) the SR144528 precursor: 5-(4-Chloro-3-methyl-phenyl)-1-(4-methyl-benzyl)-1H-pyrazole-3-carboxylic acid methyl ester ("methyl");

(b) a compound bearing the amine used in AM251 and the remainder derived from SR144528: 5-(4-Chloro-3-methyl-phenyl)-1-(4-methyl-benzyl)-1H-pyrazole-3-carboxylic acid piperidin-1-yl amide ("piperidinyl");

(c) a compound bearing the amine used in JTE-907 and the remainder derived from SR144528: 5-(4-Chloro-3-methyl-phenyl)-1-(4-methyl-benzyl)-1H-pyrazole-3-carboxylic acid (benzo[1,3]dioxol-5-yl-methyl) amide ("benzodioxo").



These analogs were studied using the Alamar Blue J774 murine macrophage viability assay, described above.

The viability assay data is shown in Figure 8.

Figure 8 is a graph of Alamar Blue J774 murine macrophage survival (% control) versus concentration of drug, for three analogs of SR144528: "methyl" (♦), "piperidinyl" (■) (n=3), and "benzodioxo" (Δ).

The three analogs ("methyl", "piperidinyl", and "benzodioxo") significantly inhibited J774 survival, with IC_{50} values of about 9 μM, about 15 μM, and about 15 μM, respectively.

These results demonstrate that derivatives related to SR144528 are highly potent against macrophages, most notably the methyl ester. This demonstrates that both esters and amides having the SR144528 skeleton are useful as highly potent drugs against macrophages and related cells.

Biological Example 7

Compound AM251 (dosage, 6 mg/kg) was investigated *in vivo* using ovariectomy induced bone loss, assessed using peripheral quantitative computed tomography, as described above.

The ovariectomy-induced bone loss data are shown in Figure 9.

Figure 9 is a bar graph showing percent changes in trabecular density, for: (a) Sham operation, no drug; (b) Sham operation, AM251 (6 mg/kg); (c) OVX operation, no drug; and (d) OVX operation, AM251 (6 mg/kg).

The data demonstrates the ability of AM251 to reverse the effects of ovariectomy-induced bone loss, and show that AM251 is very effective at reversing the bone loss seen in this model for post-menopausal osteoporosis.

Biological Example 8

Compound SR144528 (dosage, 6 mg/kg) was investigated *in vivo* using ovariectomy induced bone loss, assessed using peripheral quantitative computed tomography, as described above.

The ovariectomy-induced bone loss data are shown in Figure 10.

Figure 10 is a bar graph showing percent changes in trabecular density, for: (a) Sham operation, no drug; (b) Sham operation, SR144528 ("SR144") (6 mg/kg); (c) OVX operation, no drug; and (d) OVX operation, SR144528 ("SR144") (6 mg/kg).

The data demonstrates the ability of SR144528 to reverse the effects of ovariectomy-induced bone loss, and shows that SR144528 is very effective at reversing the bone loss seen in this model for post-menopausal osteoporosis.

Biological Example 9

Compound SR144528 (dosage, 6 mg/kg) was investigated *in vivo* using ovariectomy induced bone loss, assessed using dual energy x-ray absorptiometry as described above.

The ovariectomy-induced bone loss data are shown in Figures 11 and 12.

Figure 11 is a bar graph showing percent changes in femoral bone mineral content, for: (a) Sham operation, no drug; (b) Sham operation, SR144528 ("SR144") (6 mg/kg); (c) OVX operation, no drug; and (d) OVX operation, SR144528 ("SR144") (6 mg/kg) as measured by dual energy x-ray absorptiometry.

Figure 12 is a bar graph showing percent changes in femoral bone mineral density for (a) Sham operation, no drug; (b) Sham operation, SR144528 ("SR144") (6 mg/kg); (c) OVX operation, no drug; and (d) OVX operation, SR144528 ("SR144") (6 mg/kg) as measured by dual energy x-ray absorptiometry.

The data demonstrates the ability of SR144528 to reverse the effects of ovariectomy-induced bone loss at the femoral site, and shows that SR144528 is very effective at reversing the bone loss seen in this model for post-menopausal osteoporosis. Furthermore, it shows that SR144528 increases femoral BMC and BMD in a healthy subject, relative to control.

All of the above results demonstrate that both CB1 and CB2 inverse agonists are highly potent against osteoclasts and related cell types and have excellent potential in the treatment of osteoporosis and other bone disorders. In addition, compounds having a strong CB2 selectivity show little effect on osteoblasts, suggesting that CB2 inverse agonists, in particular, have excellent potential in the treatment of osteoporosis and other bone disorders.

* * *

The foregoing has described the principles, preferred embodiments, and modes of operation of the present invention. However, the invention should not be construed as limited to the particular embodiments discussed. Instead, the above-described embodiments should be regarded as illustrative rather than restrictive, and it should be appreciated that variations may be made in those embodiments by workers skilled in the art without departing from the scope of the present invention as described herein.

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A number of patents and publications are cited herein in order to more fully describe and disclose the invention and the state of the art to which the invention pertains. Full citations for these references are provided herein. Each of these references is incorporated herein by reference in its entirety into the present disclosure.

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CLAIMS

1. Use of a cannabinoid receptor inverse agonist or a cannabinoid receptor neutral antagonist for the manufacture of a medicament for the treatment of a bone disorder.

* * *

2. Use according to claim 1, wherein the cannabinoid receptor inverse agonist or cannabinoid receptor neutral antagonist is a CB1 inverse agonist or a CB1 neutral antagonist.

3. Use according to claim 1, wherein the cannabinoid receptor inverse agonist or cannabinoid receptor neutral antagonist is a CB2 inverse agonist or a CB2 neutral antagonist.

4. Use according to claim 1, wherein the cannabinoid receptor inverse agonist or cannabinoid receptor neutral antagonist is a CB1 inverse agonist or a CB1 neutral antagonist or a CB2 inverse agonist or a CB2 neutral antagonist.

5. Use according to claim 1, wherein the cannabinoid receptor inverse agonist or cannabinoid receptor neutral antagonist is a CB1 inverse agonist or a CB1 neutral antagonist; *and* is also a CB2 inverse agonist or a CB2 neutral antagonist.

6. Use according to claim 1, wherein the cannabinoid receptor inverse agonist or cannabinoid receptor neutral antagonist is a CB1 inverse agonist or a CB1 neutral antagonist; but is *not* a CB2 inverse agonist or a CB2 neutral antagonist.

7. Use according to claim 1, wherein the cannabinoid receptor inverse agonist or cannabinoid receptor neutral antagonist is a CB2 inverse agonist or a CB2 neutral antagonist; but is *not* a CB1 inverse agonist or a CB1 neutral antagonist.

* * *

8. Use, according to claim 1, of a cannabinoid receptor *inverse agonist* for the manufacture of a medicament for the treatment of a bone disorder.

9. Use according to claim 8, wherein the cannabinoid receptor inverse agonist is a CB1 inverse agonist.

10. Use according to claim 8, wherein the cannabinoid receptor inverse agonist is a CB2 inverse agonist.

11. Use according to claim 8, wherein the cannabinoid receptor inverse agonist is a CB1 inverse agonist or a CB2 inverse agonist.

12. Use according to claim 8, wherein the cannabinoid receptor inverse agonist is a CB1 inverse agonist; *and* is also a CB2 inverse agonist or a CB2 neutral antagonist.

13. Use according to claim 8, wherein the cannabinoid receptor inverse agonist is a CB2 inverse agonist; *and* is also a CB1 inverse agonist or a CB1 neutral antagonist.

14. Use according to claim 8, wherein the cannabinoid receptor inverse agonist is a CB1 inverse agonist; but is *not* a CB2 inverse agonist or a CB2 neutral antagonist.

15. Use according to claim 8, wherein the cannabinoid receptor inverse agonist is a CB2 inverse agonist; but is *not* a CB1 inverse agonist or a CB1 neutral antagonist.

16. Use according to any one of claims 1 to 15, wherein said cannabinoid receptor inverse agonist has a cannabinoid receptor inhibition constant (Ki) of 10 μM or less.

17. Use according to any one of claims 1 to 16, wherein said cannabinoid receptor inverse agonist stimulates cyclic AMP production with an EC50 value of 10 μM or less.

18. Use according to any one of claims 1 to 17, wherein said cannabinoid receptor inverse agonist inhibits [^{35}S]-γ-GTP binding with an IC50 value of 10 μM or less.

* * *

19. Use, according to claim 1, of a cannabinoid receptor *neutral antagonist* for the manufacture of a medicament for the treatment of a bone disorder.

20. Use according to claim 19, wherein the cannabinoid receptor neutral antagonist is a CB1 neutral antagonist.

21. Use according to claim 19, wherein the cannabinoid receptor neutral antagonist is a CB2 neutral antagonist.

22. Use according to claim 19, wherein the cannabinoid receptor neutral antagonist is a CB1 neutral antagonist or a CB2 neutral antagonist.

23. Use according to claim 19, wherein the cannabinoid receptor neutral antagonist is a CB1 neutral antagonist; and is also a CB2 inverse agonist or a CB2 neutral antagonist.

24. Use according to claim 19, wherein the cannabinoid receptor neutral antagonist is a CB2 neutral antagonist; and is also a CB1 inverse agonist or a CB1 neutral antagonist.

25. Use according to claim 19, wherein the cannabinoid receptor neutral antagonist is a CB1 neutral antagonist; but is not a CB2 inverse agonist or a CB2 neutral antagonist.

26. Use according to claim 19, wherein the cannabinoid receptor neutral antagonist is a CB2 neutral antagonist; but is not a CB1 inverse agonist or a CB1 neutral antagonist.

27. Use according to any one of claims 1 to 7 and 19 to 26, wherein said cannabinoid receptor neutral antagonist has a cannabinoid receptor inhibition constant (Ki) of 10 μM or less.

28. Use according to any one of claims 1 to 7 and 19 to 26, wherein said cannabinoid receptor neutral antagonist does not affect cyclic AMP production, but blocks the inhibition of cyclic AMP production by a cannabinoid receptor agonist with a Kb value of 10 μM or less.

29. Use according to any one of claims 1 to 7 and 19 to 26, wherein said cannabinoid receptor neutral antagonist does not affect the binding of [^{35}S]-γ-GTP, but does block the stimulation of [^{35}S]-γ-GTP binding by an agonist with a Kb value of 10 μM or less.

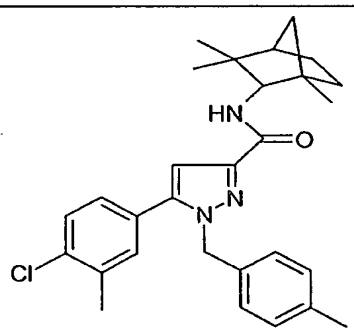
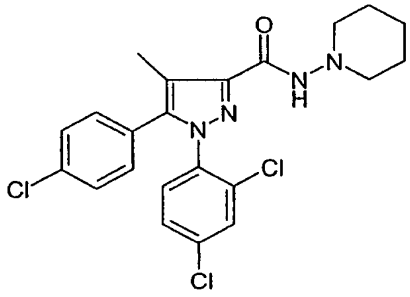
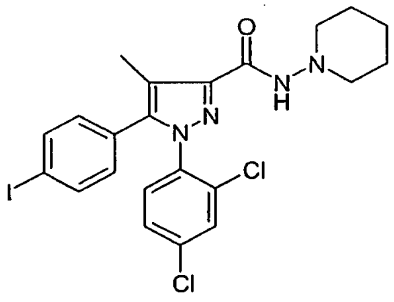
* * *

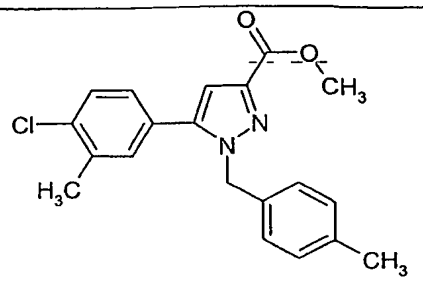
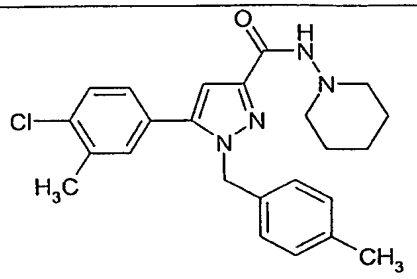
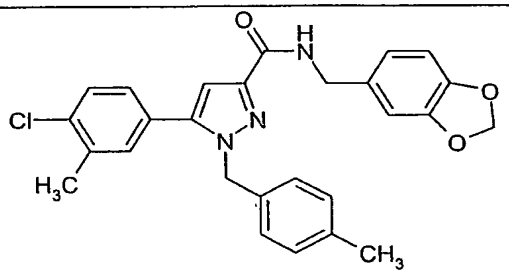
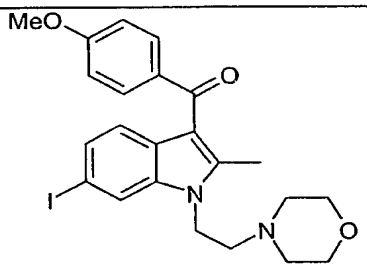
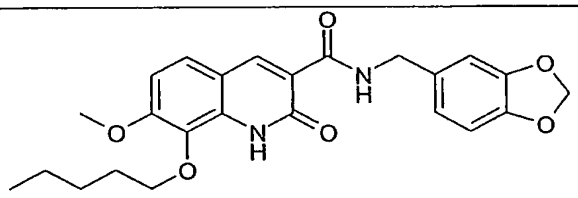
30. Use according to any one of claims 1 to 29, wherein said bone disorder is: osteoporosis which is not associated with inflammation; cancer associated bone disease; or Paget's disease of bone.

31. Use according to any one of claims 1 to 29, wherein said bone disorder is: osteoporosis associated with a genetic predisposition, sex hormone deficiency, or ageing.

* * *

32. Use according to claim 1, wherein said cannabinoid receptor inverse agonist or cannabinoid receptor neutral antagonist is selected from compounds of the following formulae, and pharmaceutically acceptable salts, solvates, amides, esters, ethers, chemically protected forms, and prodrugs thereof:

SR144528	
SR14176A	
AM251	

"methyl"	
"piperidyl"	
"benzodioxo"	
AM630	
JTE-907	

* * *

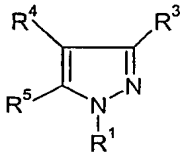
33. A method of treating a bone disorder comprising administering to a patient in need of treatment thereof a therapeutically effective amount of a cannabinoid receptor inverse agonist or a cannabinoid receptor neutral antagonist.

34. A method of treating a bone disorder according to claim 33, comprising administering to a patient in need of treatment thereof a therapeutically effective amount of a cannabinoid receptor *inverse agonist*.

35. A method of treating a bone disorder according to claim 33, comprising administering to a patient in need of treatment thereof a therapeutically effective amount of a cannabinoid receptor *neutral antagonist*.

* * *

36. Use of a compound for the manufacture of a medicament for the treatment of a bone disorder, wherein said compound is selected from compounds of the formula:



(5)

wherein:

R^1 is independently:

C_{3-20}carbocyclyl,

C_{3-20}heterocyclyl,

C_{5-20}aryl, or

C_{5-20}aryl-C_{1-4}alkyl;

and is optionally substituted;

R^4 is independently:

-H,

C_{1-4}alkyl,

C_{3-20}heterocyclyl,

C_{5-20}aryl, or

C_{5-20}aryl-C_{1-4}alkyl;

and is optionally substituted;

R^5 is independently:

C_{1-4}alkyl,

C_{3-20}carbocyclyl,

C_{3-20}heterocyclyl,

C_{5-20}aryl, or

C_{5-20}aryl-C_{1-4}alkyl;

and is optionally substituted;

R^3 is independently:

amino-acyl;

amino-amino-acyl;

acyl;

acyl-oxy;

ether; or

and is optionally substituted;

and stereoisomers thereof;

and pharmaceutically acceptable salts, solvates, amides, esters, ethers, chemically protected forms, and prodrugs thereof.

* * *

37. Use according to claim 36, wherein R^3 is independently amino-acyl; and is optionally substituted.

38. Use according to claim 36, wherein R^3 is independently:
C_{3-8}cycloamino-acyl,
C_{3-20}carbocyclyl-amino-acyl,
C_{3-20}heterocyclyl-amino-acyl,
C_{1-7}alkyl-amino-acyl,
C_{5-20}aryl-amino-acyl,
C_{5-20}aryl-C_{1-7}alkyl-amino-acyl,
C_{5-20}heteroarylamino-acyl
and is optionally substituted.

39. Use according to claim 36, wherein R^3 is independently C_{3-8}cycloamino-acyl; and is optionally substituted.

40. Use according to claim 36, wherein R^3 is independently piperidino-acyl, piperazino-acyl, morpholino-acyl, azepino-acyl; and is optionally substituted.

41. Use according to claim 36, wherein R^3 is independently C_{3-20}carbocyclyl-amino-acyl; and is optionally substituted.

42. Use according to claim 36, wherein R^3 is independently C_{1-7}alkyl-amino-acyl; and is optionally substituted.

43. Use according to claim 36, wherein R^3 is independently C_{5-20}aryl-amino-acyl; and is optionally substituted.

44. Use according to claim 36, wherein R^3 is independently phenyl-amino-acyl; and is optionally substituted.

45. Use according to claim 36, wherein R^3 is independently C_{5-20}aryl-C_{1-7}alkyl-amino-acyl; and is optionally substituted.

46. Use according to claim 36, wherein R^3 is independently benzyl-amino-acyl; and is optionally substituted.

47. Use according to claim 36, wherein R^3 is independently C_{5-20}heteroarylamino-acyl; and is optionally substituted.

48. Use according to claim 36, wherein R^3 is independently pyrrolo-acyl; and is optionally substituted.

* * *

49. Use according to claim 36, wherein R^3 is independently amino-amino-acyl; and is optionally substituted.

50. Use according to claim 36, wherein R^3 is independently:
C_{3-8}cycloamino-amino-acyl,
C_{3-20}carbocyclyl-amino-amino-acyl,
C_{3-20}heterocyclyl-amino-amino-acyl,
C_{1-7}alkyl-amino-amino-acyl,
C_{5-20}aryl-amino-amino-acyl,
C_{5-20}aryl-C_{1-7}alkyl-amino-amino-acyl,
C_{5-20}heteroarylamino-amino-acyl,
and is optionally substituted.

51. Use according to claim 36, wherein R^3 is independently C_{3-8}cycloamino-amino-acyl; and is optionally substituted.

52. Use according to claim 36, wherein R^3 is independently:
piperidino-amino-acyl, piperazino-amino-acyl, morpholino-amino-acyl, or azepino-amino-acyl; and is optionally substituted.

53. Use according to claim 36, wherein R^3 is independently:
C_{5-20}aryl-amino-amino-acyl,
C_{5-20}aryl-C_{1-7}alkyl-amino-amino-acyl, or
C_{5-20}heteroarylamino-amino-acyl;
and is optionally substituted.

54. Use according to claim 36, wherein R^3 is independently phenyl-amino-amino-acyl, benzyl-amino-amino-acyl, or pyrrolo-amino-acyl; and is optionally substituted.

* * *

55. Use according to claim 36, wherein R^3 is independently acyl; and is optionally substituted.

56. Use according to claim 36, wherein R^3 is independently:
C_{1-7}alkyl-acyl,
C_{5-20}aryl-acyl, or
C_{5-20}aryl-C_{1-7}alkyl-acyl;
and is optionally substituted.

57. Use according to claim 36, wherein R^3 is independently:
C_{5-20}aryl-acyl, or
C_{5-20}aryl-C_{1-7}alkyl-acyl,
and is optionally substituted.

58. Use according to claim 36, wherein R^3 is independently phenyl-acyl, and is optionally substituted.

59. Use according to claim 36, wherein R^3 is independently benzyl-acyl, and is optionally substituted.

* * *

60. Use according to claim 36, wherein R^3 is independently acyl-oxy; and is optionally substituted.

61. Use according to claim 36, wherein R^3 is independently:
C_{1-7}alkyl-acyl-oxy,
C_{5-20}aryl-acyl-oxy, or
C_{5-20}aryl-C_{1-7}alkyl-acyl-oxy;
and is optionally substituted.

62. Use according to claim 36, wherein R^3 is independently:
C_{5-20}aryl-acyl-oxy, or
C_{5-20}aryl-C_{1-7}alkyl-acyl-oxy,
and is optionally substituted.

63. Use according to claim 36, wherein R^3 is independently phenyl-acyl-oxy, and is optionally substituted.

64. Use according to claim 36, wherein R^3 is independently benzyl-acyl-oxy, and is optionally substituted.

* * *

65. Use according to claim 36, wherein R^3 is independently ether; and is optionally substituted.

66. Use according to claim 36, wherein R^3 is independently:
C_{1-7}alkyl-oxy,
C_{5-20}aryl-oxy, or
C_{5-20}aryl-C_{1-7}alkyl-oxy;
and is optionally substituted.

67. Use according to claim 36, wherein R^3 is independently C_{1-7}alkoxy; and is optionally substituted.

68. Use according to claim 36, wherein R^3 is independently: -O-Me, -O-Et, -O-nPr, -O-iPr, -O-nBu, -O-sBu, -O-iBu, -O-tBu, or -O-nPe.

* * *

69. Use according to any one of claims 36 to 68, wherein R^1 is independently C_{5-20}aryl or C_{5-20}aryl-C_{1-4}alkyl; and is optionally substituted.

70. Use according to any one of claims 36 to 68, wherein R^1 is independently phenyl or benzyl; and is optionally substituted.

71. Use according to any one of claims 36 to 68, wherein R^1 is independently C_{5-20}aryl; and is optionally substituted.

72. Use according to any one of claims 36 to 68, wherein R^1 is independently C_{5-7}aryl; and is optionally substituted.

73. Use according to any one of claims 36 to 68, wherein R^1 is independently phenyl; and is optionally substituted.

74. Use according to any one of claims 36 to 68, wherein R^1 is independently C_{5-20}aryl-C_{1-4}alkyl; and is optionally substituted.

75. Use according to any one of claims 36 to 68, wherein R^1 is independently C_{5-7}aryl-C_{1-4}alkyl; and is optionally substituted.

76. Use according to any one of claims 36 to 68, wherein R^1 is independently C_6aryl-C_{1-4}alkyl; and is optionally substituted.

77. Use according to any one of claims 36 to 68, wherein R^1 is independently benzyl; and is optionally substituted.

* * *

78. Use according to any one of claims 36 to 77, wherein R^5 is independently C_{5-20}aryl or C_{5-20}aryl-C_{1-4}alkyl; and is optionally substituted.

79. Use according to any one of claims 36 to 77, wherein R^5 is independently phenyl or benzyl; and is optionally substituted.

80. Use according to any one of claims 36 to 77, wherein R^5 is independently C_{5-20}aryl; and is optionally substituted.

81. Use according to any one of claims 36 to 77, wherein R^5 is independently C_{5-7}aryl; and is optionally substituted.

82. Use according to any one of claims 36 to 77, wherein R^5 is independently phenyl; and is optionally substituted.

83. Use according to any one of claims 36 to 77, wherein R^5 is independently C_{5-20}aryl-C_{1-4}alkyl; and is optionally substituted.

84. Use according to any one of claims 36 to 77, wherein R^5 is independently C_{5-7}aryl-C_{1-4}alkyl; and is optionally substituted.

85. Use according to any one of claims 36 to 77, wherein R^5 is independently C_6aryl-C_{1-4}alkyl; and is optionally substituted.

86. Use according to any one of claims 36 to 77, wherein R^5 is independently benzyl; and is optionally substituted.

87. Use according to any one of claims 36 to 77, wherein R^5 is independently C_{1-4}alkyl; and is optionally substituted.

88. Use according to any one of claims 36 to 77, wherein R^5 is independently -Me, -Et, -nPr, -iPr, -nBu, -sBu, -iBu, -tBu, or -nPe.

* * *

89. Use according to any one of claims 36 to 68, wherein R^1 is independently C_{5-20}aryl-C_{1-4}alkyl, and is optionally substituted and R^5 is independently C_{5-20}aryl, and is optionally substituted.

90. Use according to any one of claims 36 to 68, wherein R^1 is independently benzyl, and is optionally substituted and R^5 is independently phenyl, and is optionally substituted.

91. Use according to any one of claims 36 to 68, wherein R^1 is independently C_{5-20}aryl, and is optionally substituted, and R^5 is independently C_{5-20}aryl-C_{1-4}alkyl, and is optionally substituted.

92. Use according to any one of claims 36 to 68, wherein R^1 is independently phenyl, and is optionally substituted, and R^5 is independently benzyl, and is optionally substituted.

93. Use according to any one of claims 36 to 68, wherein R^1 is independently C_{5-20}aryl, and is optionally substituted and R^5 is independently C_{5-20}aryl, and is optionally substituted.

94. Use according to any one of claims 36 to 68, wherein R^1 is independently phenyl, and is optionally substituted and R^5 is independently phenyl, and is optionally substituted.

* * *

95. Use according to any one of claims 36 to 94, wherein R^4 is independently C_{1-4}alkyl; and is optionally substituted.

96. Use according to any one of claims 36 to 94, wherein R^4 is independently C_{3-20}heterocyclyl; and is optionally substituted.

97. Use according to any one of claims 36 to 94, wherein R^4 is independently C_{5-7}aryl; and is optionally substituted.

98. Use according to any one of claims 36 to 94, wherein R^4 is independently phenyl; and is optionally substituted.

99. Use according to any one of claims 36 to 94, wherein R^4 is independently C_{5-7}aryl-C_{1-4}alkyl; and is optionally substituted.

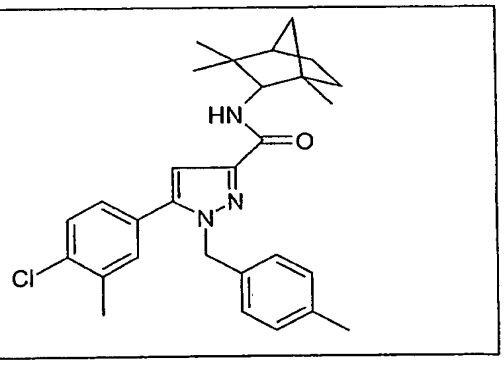
100. Use according to any one of claims 36 to 94, wherein R^4 is independently benzyl; and is optionally substituted.

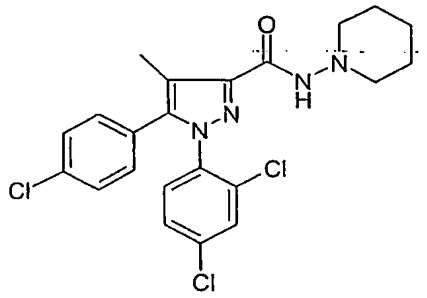
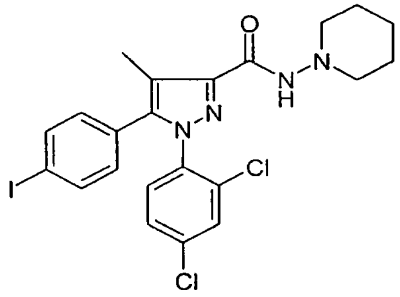
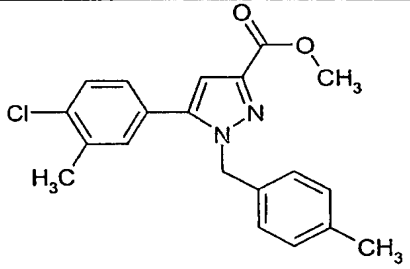
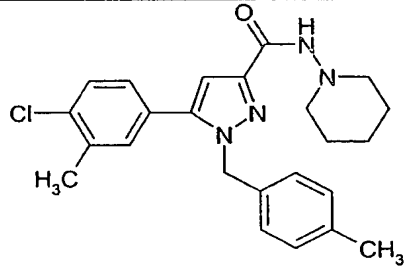
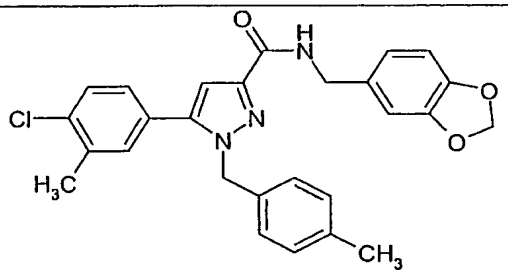
101. Use according to any one of claims 36 to 94, wherein R^4 is independently -H, -Me, -Et, -Ph, or -CH_2Ph.

102. Use according to any one of claims 36 to 94, wherein R^4 is independently -H.

* * *

103. Use according to claim 36, wherein the compound is selected from the following, and pharmaceutically acceptable salts, solvates, amides, esters, ethers, chemically protected forms, and prodrugs thereof:

SR144528	

SR14176A	
AM251	
"methyl"	
"piperidyl"	
"benzodioxo"	

* * *

104. Use according to any one of claims 36 to 103, wherein said bone disorder is: osteoporosis not associated with inflammation; cancer associated bone disease; or Paget's disease of bone.

105. Use according to any one of claims 36 to 103, wherein said bone disorder is: osteoporosis associated with a genetic predisposition, sex hormone deficiency, or ageing.

* * *

106. A method of treating a bone disorder comprising administering to a patient in need of treatment thereof a therapeutically effective amount of a compound as defined in any one of claims 36 to 103.

107. A method according to claim 106, wherein said bone disorder is: osteoporosis not associated with inflammation; cancer associated bone disease; or Paget's disease of bone.

108. A method according to claim 106, wherein said bone disorder is: osteoporosis associated with a genetic predisposition, sex hormone deficiency, or ageing.

FIGURE 1

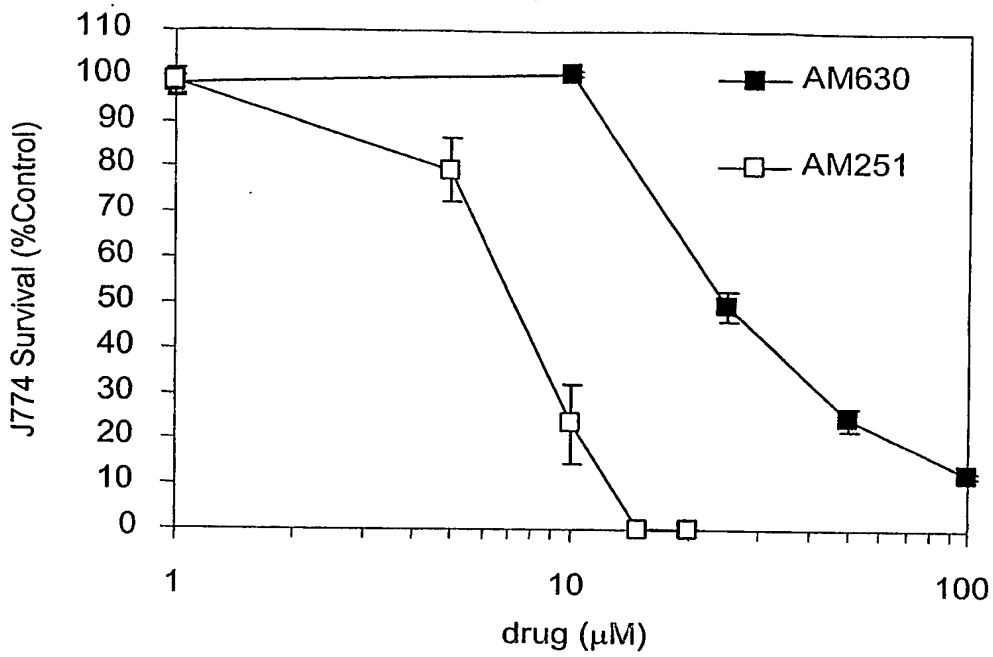


FIGURE 2

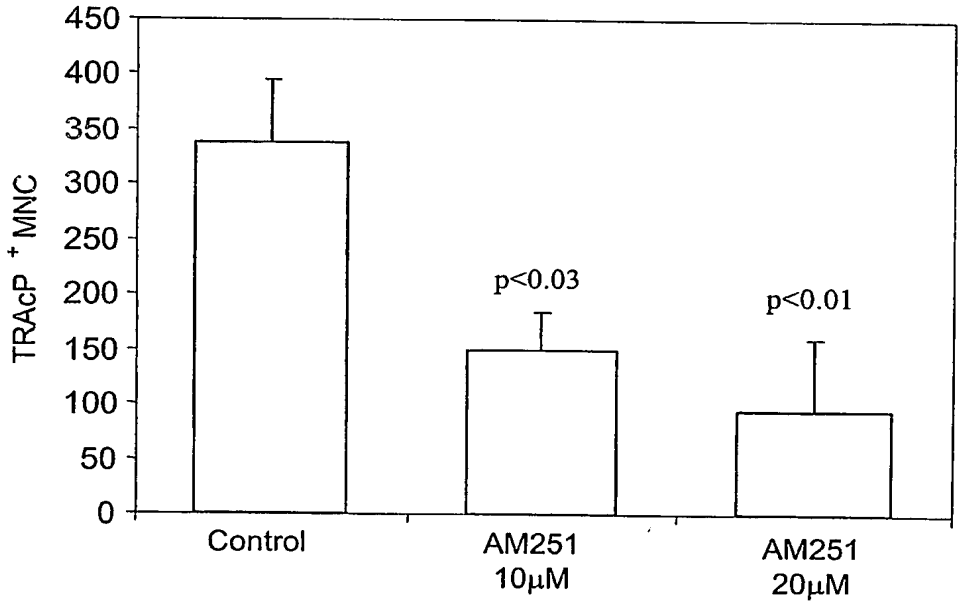


FIGURE 3

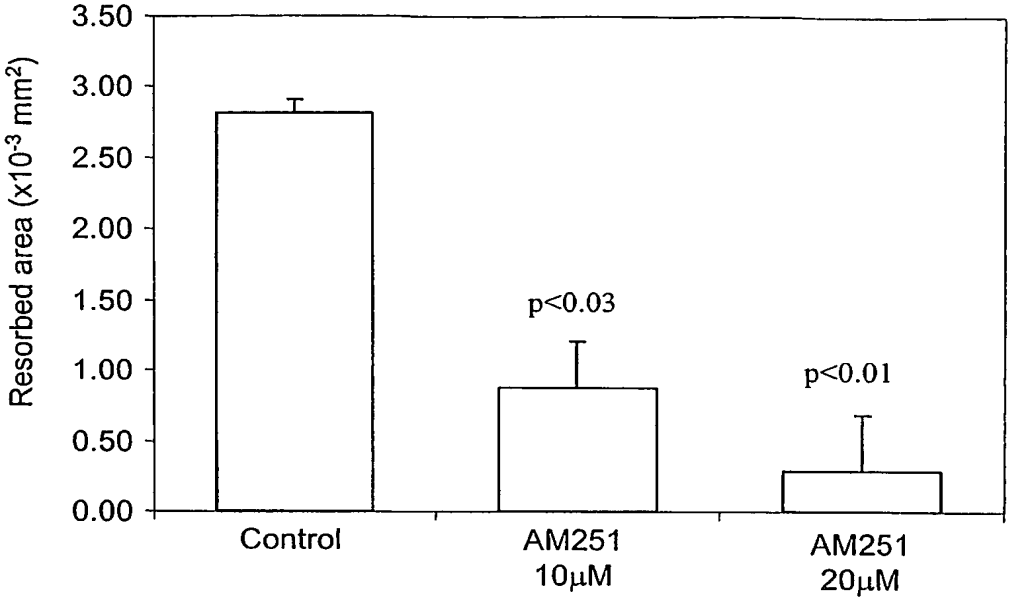


FIGURE 4

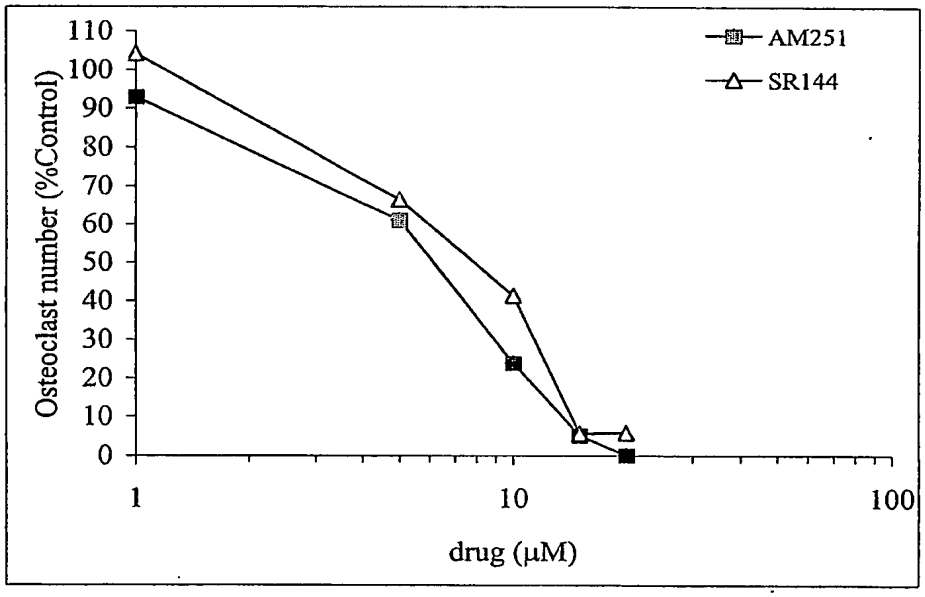


FIGURE 5

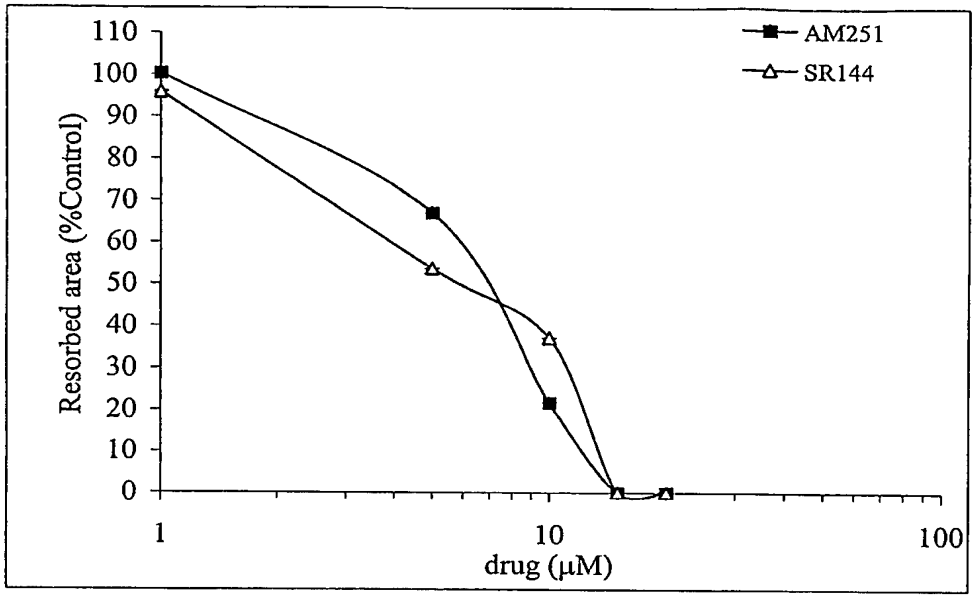


FIGURE 6

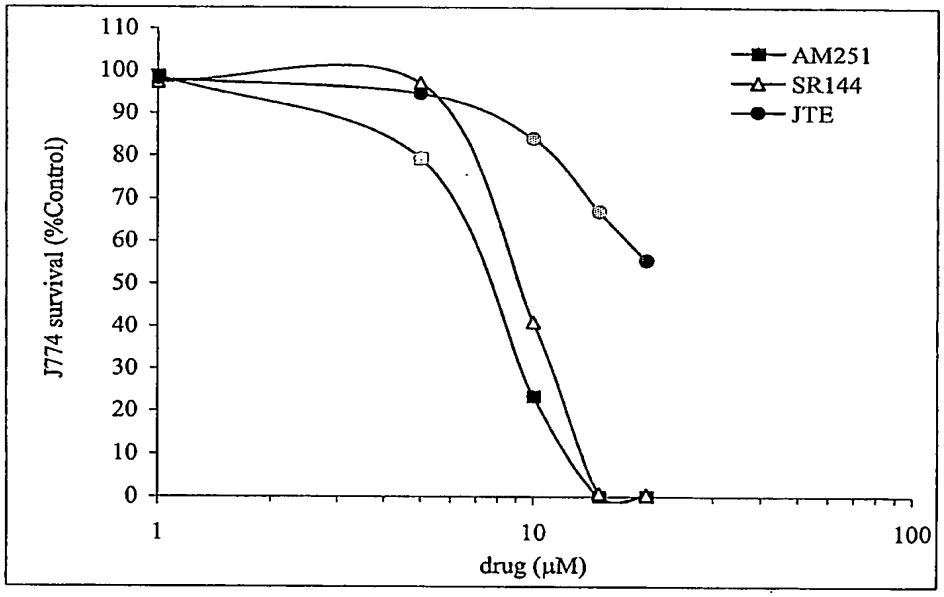


FIGURE 7

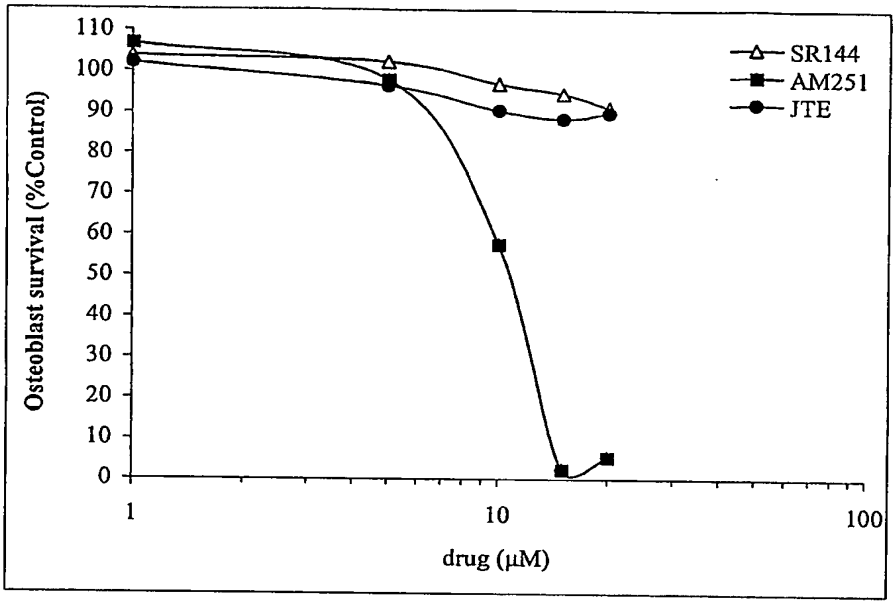


FIGURE 8

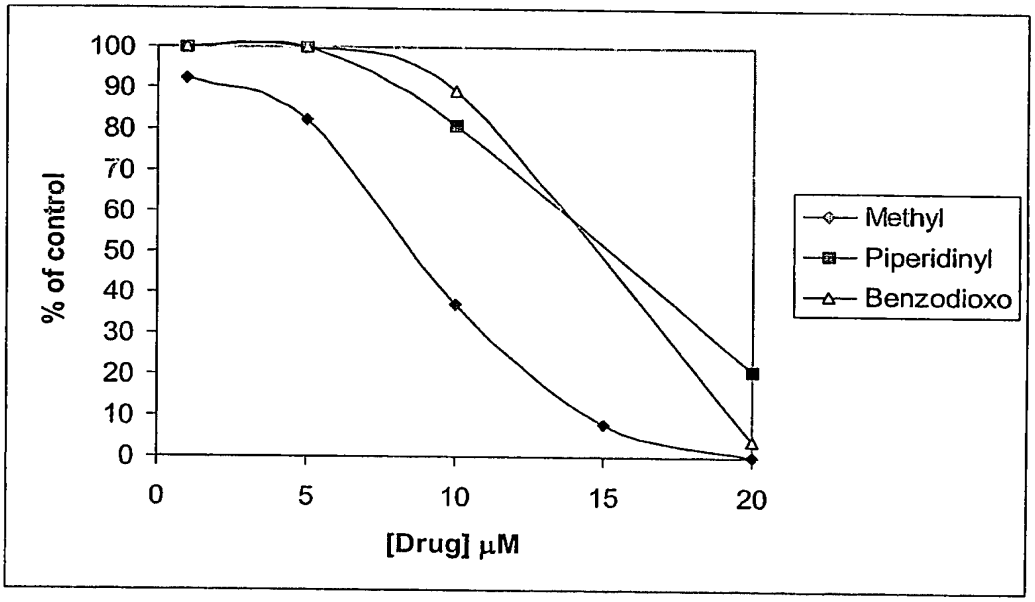


FIGURE 9

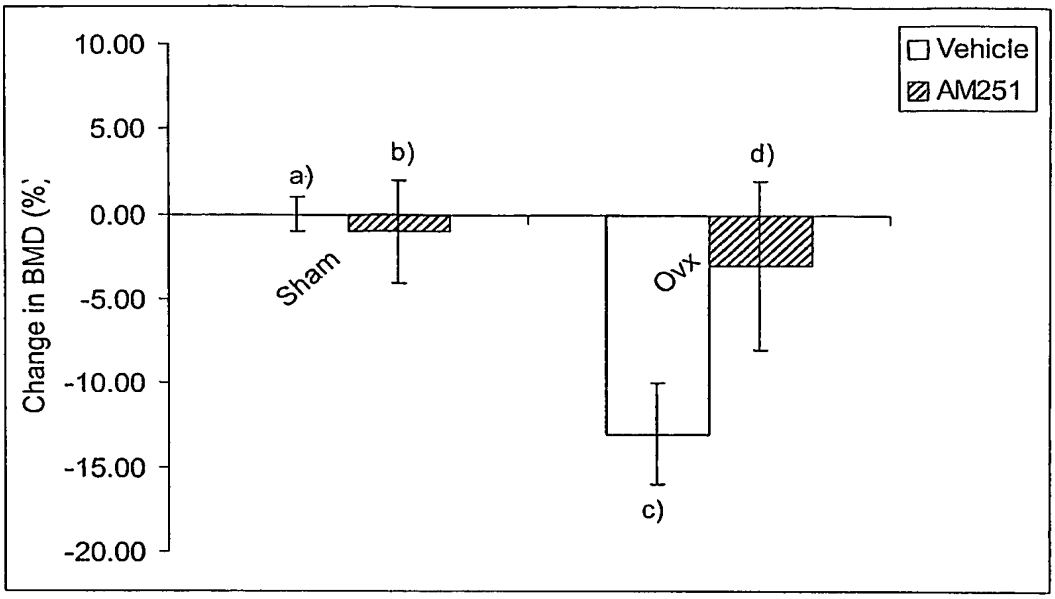


FIGURE 10

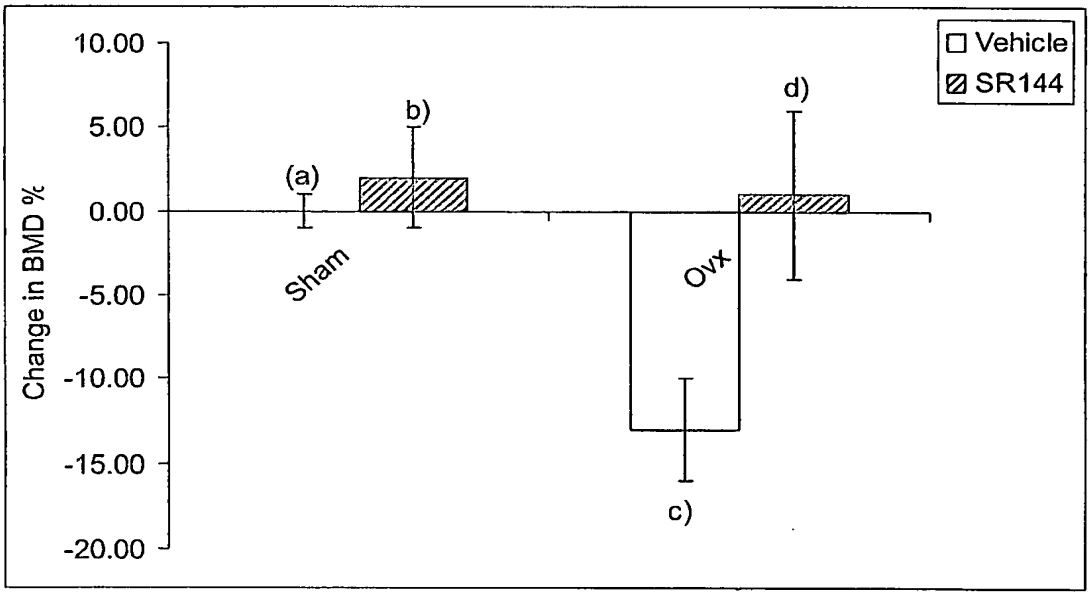


FIGURE 11

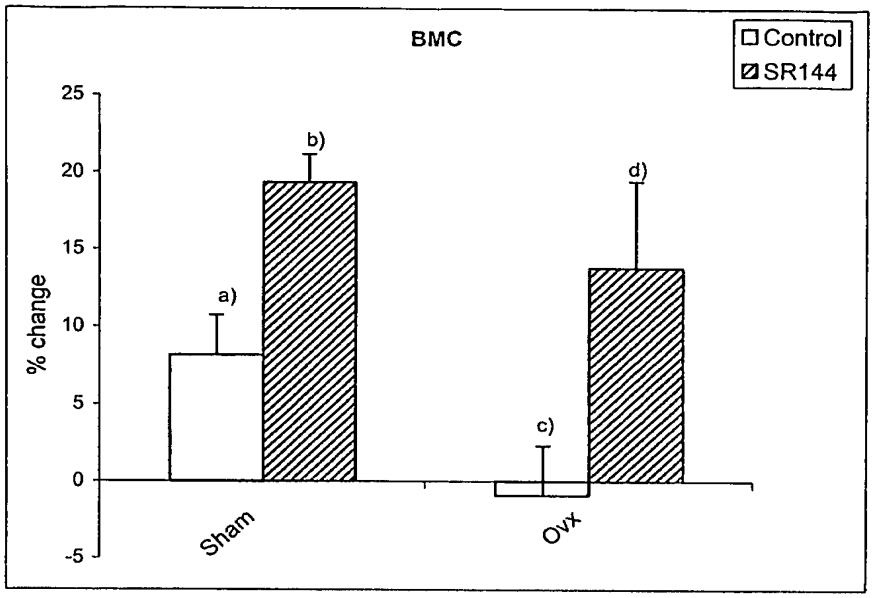
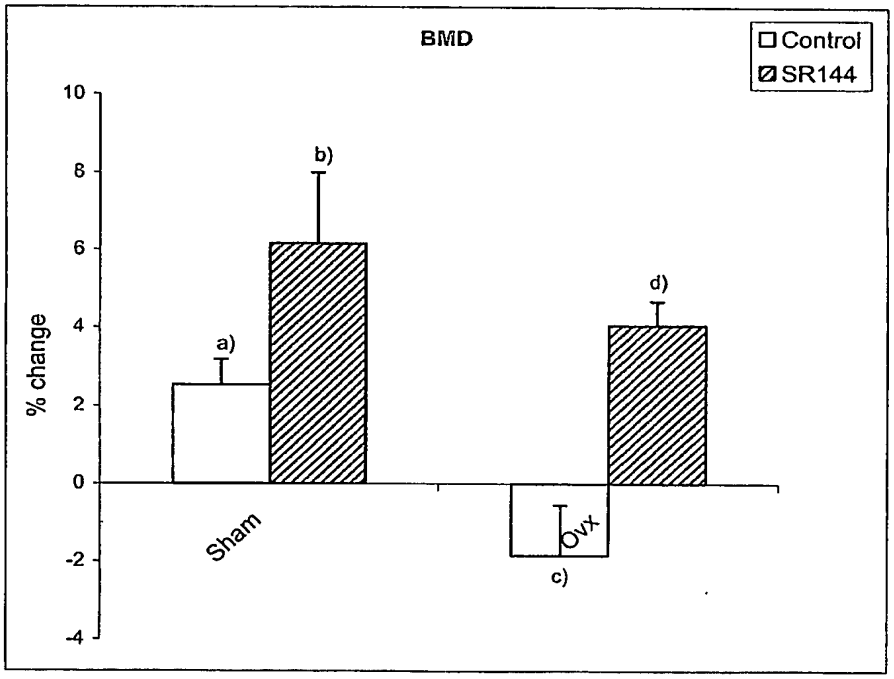


FIGURE 12



INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB2004/000858

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61P19/08 A61P19/10 A61K31/415 A61K31/454 A61K31/5377 A61K31/4709

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00/32189 A (GAO DANCHEN ; SEARLE & CO (US); MAZHARY AHMAD M (US); HLINAK ANTHONY J) 8 June 2000 (2000-06-08) page 5, lines 8-13 page 9, lines 15-17 page 10, lines 23-25 page 11, line 31 - page 12, line 3	1,30,31, 33
A	WO 01/96330 A (SCHERING CORP) 20 December 2001 (2001-12-20) claims 9-11	1-31, 33-35
A	WO 98/31227 A (CHRISTENSEN SIEGFRIED B ; ELLIOTT JOHN DUNCAN (US); SMITHKLINE BEECHAM) 23 July 1998 (1998-07-23) claims 1,9,10,12,14	1-31, 33-35

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 May 2004	05/08/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Tardi, C

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB2004/000858

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99/26612 A (CHRISTENSEN SIEGFRIED B ; SMITHKLINE BEECHAM CORP (US); BENDER PAUL E) 3 June 1999 (1999-06-03) page 4, lines 5-11; claims 1,3	1-31, 33-35
A	WO 98/41519 A (CHRISTENSEN SIEGFRIED B ; SMITHKLINE BEECHAM CORP (US); BENDER PAUL EL) 24 September 1998 (1998-09-24) page 3, lines 3-7; claims 1,9,11	1-31, 33-35
X	US 6 294 558 B1 (KATO TOMOKI ET AL) 25 September 2001 (2001-09-25) column 10, lines 24-31; claims 2,26-29; examples 130-134	1,30,31, 33, 36-38, 40,42, 55, 69-73, 78-82, 93,94, 101,102, 104-108
A	GOYA P ET AL: "Recent advances in cannabinoid receptor agonists and antagonists" EXPERT OPINION ON THERAPEUTIC PATENTS 2000 UNITED KINGDOM, vol. 10, no. 10, 2000, pages 1529-1538, XP002282106 ISSN: 1354-3776 page 1534, column 1, line 3 - column 2, line 15	1-35
A	BARTH F: "Cannabinoid receptor agonists and antagonists" EXPERT OPINION ON THERAPEUTIC PATENTS 1998 UNITED KINGDOM, vol. 8, no. 3, 1998, pages 301-313, XP002282107 ISSN: 1354-3776 the whole document	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2004/000858

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 33-35 and 106-108 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB2004/000858

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
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INTERNATIONAL SEARCH REPORT

Information on patent family members

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PCT/GB2004/000858

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